VOLUME XVIII NUMBER 5

DISEASES

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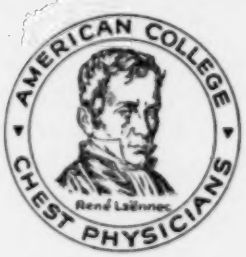

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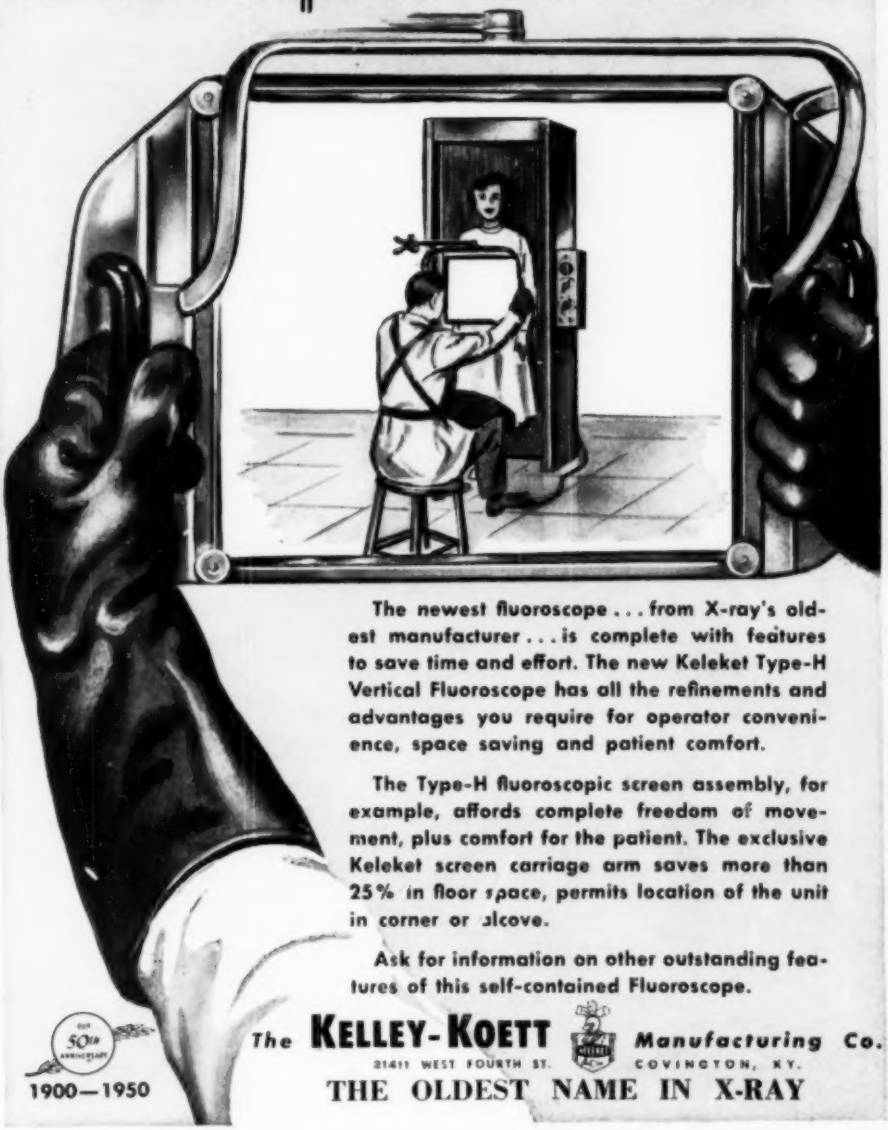

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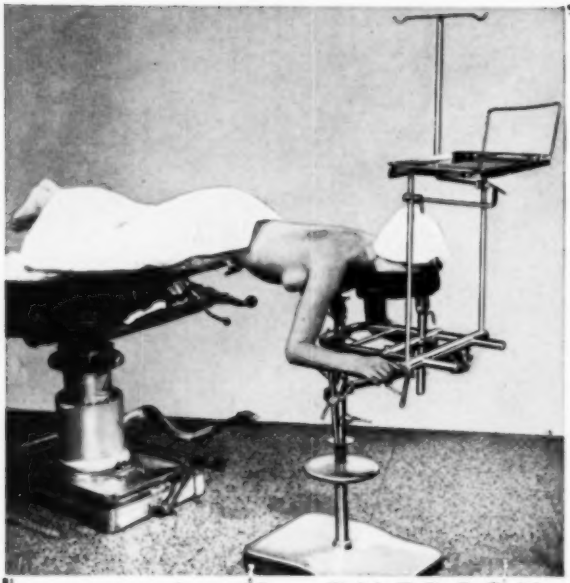

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VOL. XVIII NOVEMBER 1950 No. 5

CONTENTS:

EXTRAPERIOSTEAL TEMPORARY PLOMBAGE IN THORACOPLASTY: A PRELIMINARY REPORT 401
Francis M. Woods, M.D., James H. Walker, M.D. and Ivan Schmidt, M.D., Boston, Massachusetts

PRELIMINARY REPORT OF CLINICAL EXPERIENCE WITH P-AMINOSALICYLIC ACID 413
Nicholas H. DeJanney, M.D., John Cox, M.D. and Ellen Grindell-Balchum, M.D., Detroit, Michigan

STUDIES ON THE BEHAVIOR OF PARA-AMINOSALICYLIC ACID IN TUBERCULOUS PLEURAL EFFUSIONS 430
S. H. Lawrence, M.D. and Nathaniel Comden, M.D., San Fernando, California

AEROSOLS II: THE ROLE OF PARTICLE SIZE IN INHALATION THERAPY BY ATOMIZATION AND BY PENICILLIN DUSTS 435
Harold A. Abramson, M.D., New York, New York

ASPIRATION OF PLEURAL FLUID 450
Morris Braverman, M.D., Detroit, Michigan

NON-BACTERIAL PNEUMONIAS 456
Jerome T. Syverton, M.D., Minneapolis, Minnesota

MEDICAL MANAGEMENT OF ACUTE LUNG ABSCESS REPORT OF 12 CASES 478
Jim S. Jewett, M.D. and George E. Dimond, M.D., Dearborn, Michigan

THE BCG CONTROVERSY 502
Lloyd B. Dickey, M.D., San Francisco, California

TUBERCULOSIS CONTROL IN INSTITUTIONS FOR THE MENTALLY ILL 508
Edmund W. Miller, M.D., Anoka, Minnesota

COLLEGE NEWS 515

COLLEGE CHAPTER NEWS 517

BOOK REVIEW 518
Comment: Godias J. Drolet

MEDICAL SERVICE BUREAU 520

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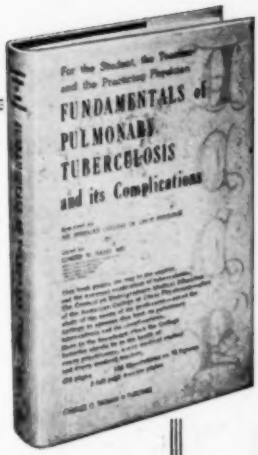
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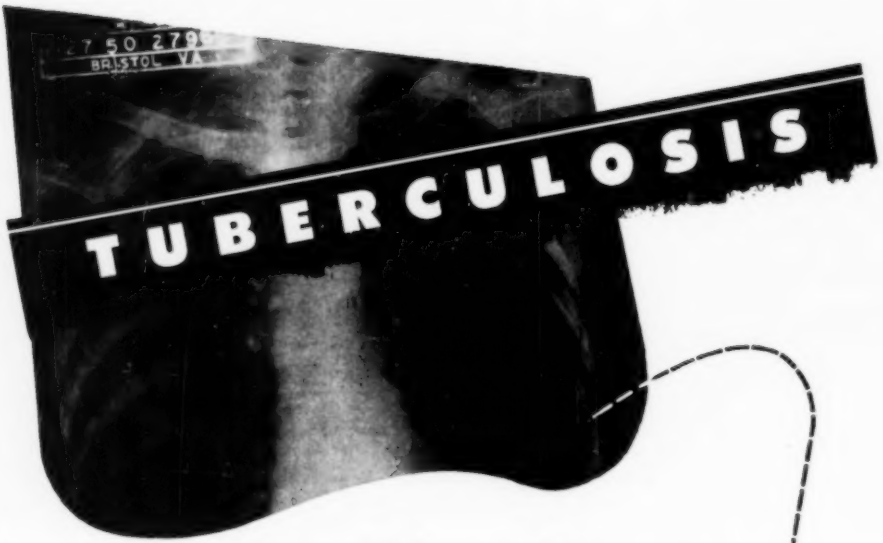

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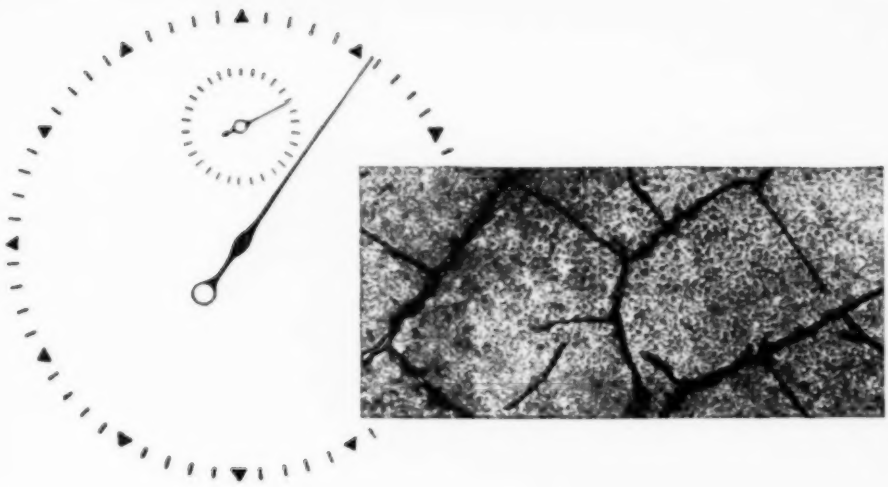

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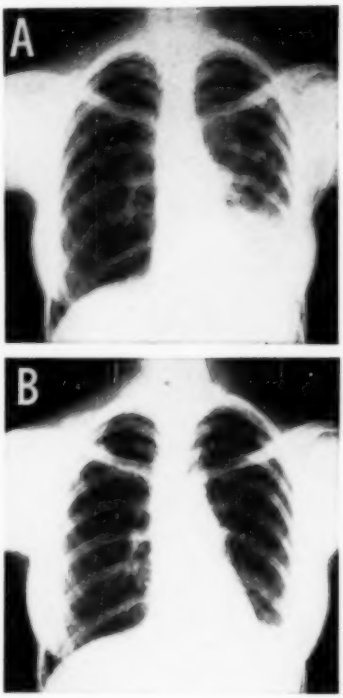

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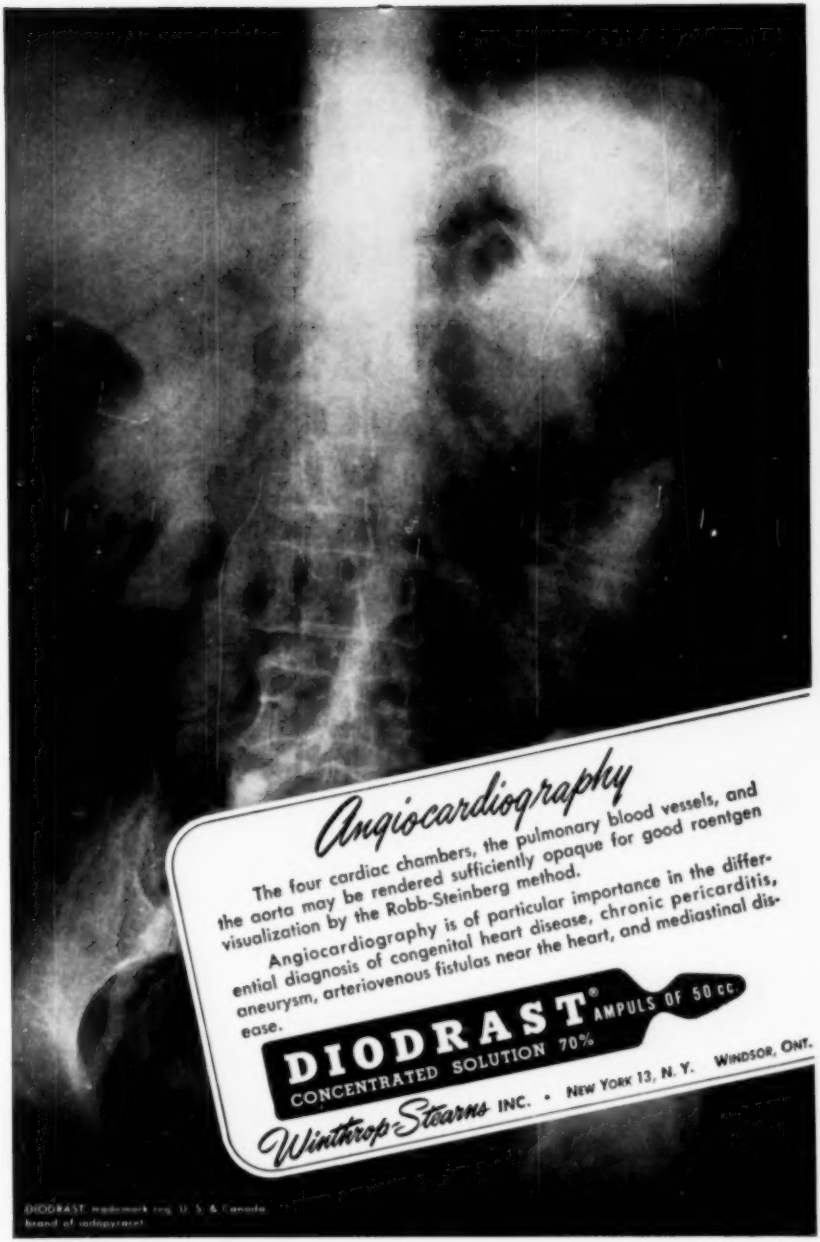
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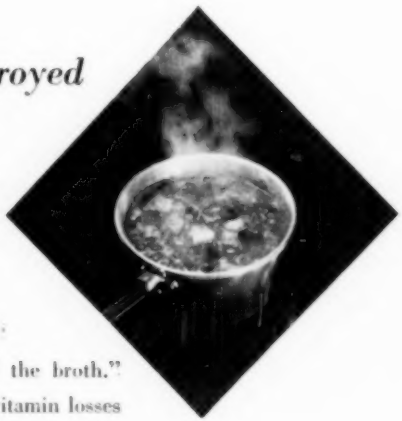

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DISEASES *of the* CHEST

VOL. XVIII NOVEMBER 1950 NUMBER 5

Extraperiosteal Temporary Plombage in Thoracoplasty: A Preliminary Report*

FRANCIS M. WOODS, M.D., JAMES H. WALKER, M.D. and IVAN SCHMIDT, M.D.
Boston, Massachusetts

Continuing changes in thoracoplasty indicate its shortcomings in the treatment of pulmonary tuberculosis. Although the modern multistage thoracoplasty has been extremely effective, it requires a series of two to five operative procedures associated with considerable physical setback, psychic trauma, pain, and long hospitalization and expense. It has been recognized that a better degree of collapse could be obtained if the entire thoracoplasty could be performed at one operation. However, the extent of each stage is limited by the flaccidity of the chest wall with resulting paradoxical motion, anoxemia, and difficulty in raising secretions. Some degree of revision is usually needed at each successive stage.

We have devised an efficient two-stage modification of the standard thoracoplasty using temporary extraperiosteal plombage. In the past air, fluid, and gauze have been used outside the flaccid chest wall as plombage materials. All have been abandoned because of infection or tissue reaction. It first occurred to one of us (I.S.) that a plastic material known to produce minimal tissue reaction might be used successfully as an extraperiosteal plombage. We therefore planned an operation to substitute for multistage thoracoplasty in which, at a first stage, the periosteum is stripped from all the ribs that would have been removed in all the stages of a thoracoplasty. The ribs themselves are not removed. A pack of plastic material is placed between the denuded ribs on the outside and the intercostal bundles and rib beds on the inside. Thus the latter are held in a depressed position and the underlying lung in a collapsed state. The rigidity of the pack and the overlying

*From the Overholt Thoracic Clinic and the Department of Surgery, Tufts College Medical School.

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ribs prevent any paradoxical motion of the chest wall. The chest wall muscles and skin are re-approximated. An interval of time is allowed to elapse during which fibrosis and bone regeneration from the periosteum produces sufficient rigidity to prevent paradox. A second stage is then performed during which the denuded ribs and the plastic material are removed. In this way it was planned to complete in two stages what ordinarily is accomplished in two to five stages.

Operative Procedure

The patient is placed in the lateral position on the operating table and the usual curved parascapular incision is made as for an ordinary thoracoplasty (Fig. 1).

The chest wall muscles are divided, the scapula retracted, and the attachment of the serratus magnus separated from the second, third, and fourth ribs. The extent of the desired collapse is noted by reviewing the x-rays (Fig. 2). The bodies of the ribs are deperiostealized up through the second rib (Fig. 3). The posterior gutter is freed by severing the attachments of the transverse processes and stripping the periosteum from the heads of the ribs (Fig. 4). The intercostal muscles are completely separated from the paraspinal muscles. The anterior portion of the collapse is fashioned by extending the periosteal separation to the desired points. It is possible to dissect around to the sternum on the second and third ribs (Fig. 5). This sequence of dissection now allows maximum freedom in separating the periosteum from the under surface of the first rib (Fig. 6). The upper surface is not disturbed at this stage to avoid trauma to the brachial plexus and vessels. It is necessary to secure complete hemostasis. The wound is lavaged well with saline. The extraperiosteal space, created between the

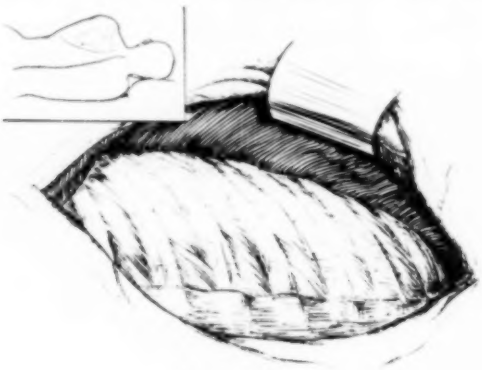

FIGURE 1

denuded ribs externally and the depressed periosteum and intercostal bundles internally, is now filled with leucite spheres* (Fig. 7). Spheres one and one fourth inches in diameter are most satisfactory but spheres have been used ranging from one to two inches in diameter. Care is taken that the collapse is adequate both anteriorly and in the posterior gutter. The number of spheres is recorded. Streptomycin and penicillin is placed in the operative space and the wound is closed in layers.

The interval between stages is determined at this time by an

*The leucite spheres are prepared by scrubbing with soap and water, soaking for 48 hours or more in 1/1000 Zephrian solution, and rinsing in saline just before using.

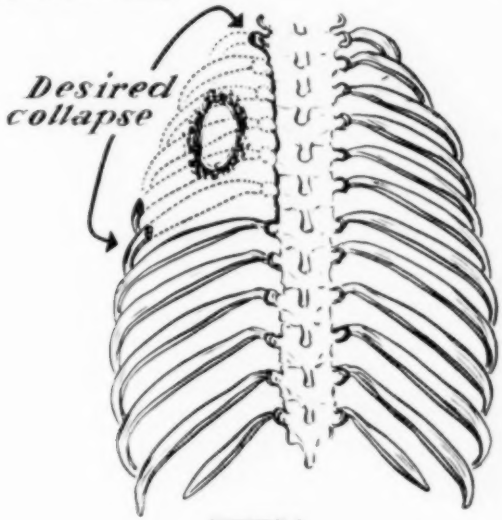

FIGURE 2

FIGURE 3

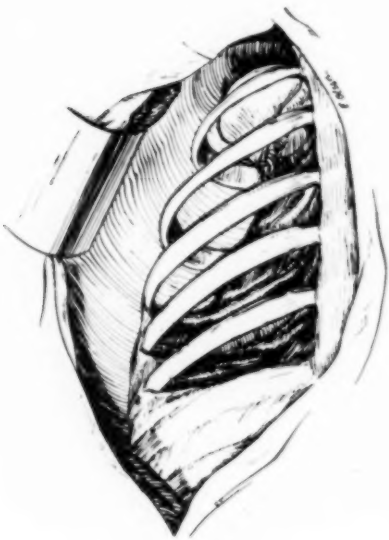

FIGURE 5

FIGURE 4

FIGURE 7

FIGURE 6

FIGURE 9

FIGURE 8

evaluation of the following factors: (1) Flaccidity of the lung as palpated and observed, (2) amount of sputum and (3) cardiopulmonary reserve. The usual interval is two and a half to six weeks. The minimum time, two and one-half weeks, is used only in a good-risk patient without extensive disease, or large amounts of secretions, and with a relatively firm underlying lung and pleura. Patients over 50 rarely have adequate cardiopulmonary reserve to tolerate any degree of paradox; in them, the interval should probably never be less than four weeks.

At the second stage, the incision is re-opened. Variable amounts of fibrin and serum surround the leucite balls and the deperiostealized ribs (Fig. 8). Central portions of all these ribs except the first are resected. The balls are removed (Fig. 9), exposing the periosteal bed which is stiff enough to prevent significant paradoxical motion. Slight depressions caused by the balls are noted. Fibrin is freed from the transverse processes to the level of the spine where the transverse processes and the ribs are severed (Fig. 10). The anterior ends of the ribs are divided as far forward as desired. Complete removal of the first rib is readily done through this wide exposure (Fig. 11). This completes the thoracoplasty (Fig. 12) and the wound is closed.

Case Selection

This is an unselected group of 76 patients having indications for multistage thoracoplasty. As experience accrued, it became

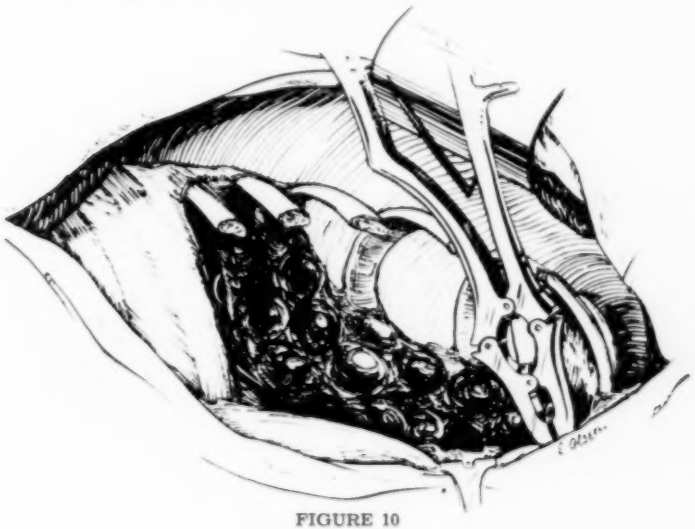

FIGURE 10

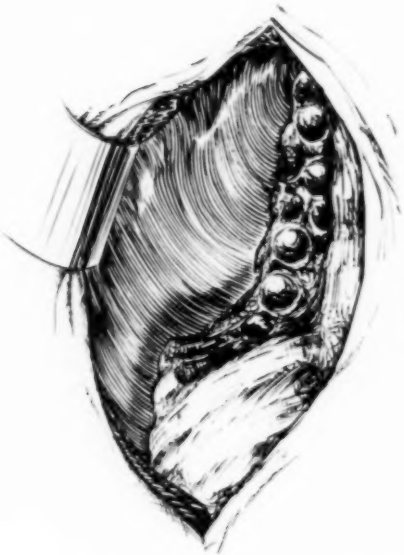

FIGURE 12

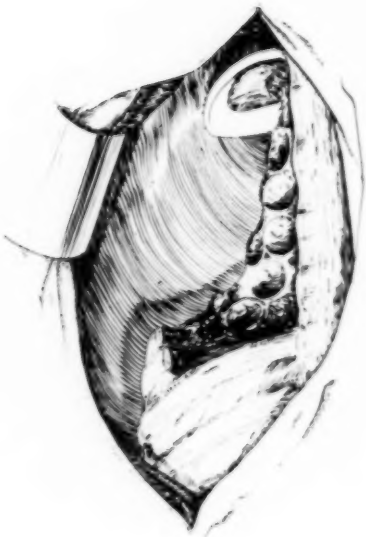

FIGURE 11

evident that desperate risk patients, formerly denied thoracoplasty, could now safely be given permanent collapse therapy. Age varied from 18 to 64 with 16 between 50 and 59, and five being 60 or over. All patients had cavitary disease and positive sputum. Twenty-one had cavities of four to six cm. in size; five over six cm.; and 12 had bilateral cavitary disease. Associated diseases included the following: extrapulmonary tuberculosis, pernicious anemia, silicosis, retrobulbar neuritis, multiple sclerosis, nephritis, diabetes mellitus, hypertension, asthma, and peptic ulcer. Three had contralateral pneumothorax and one had contralateral thoracoplasty at the time of surgery.

Results

The sputum conversion figures on the 43 patients followed three months or longer after the second stage are noted in Table I. Ten of these have already been discharged from their sanatoria as arrested. Figures are based on sputum concentrates and/or gastric cultures.

Excluding patients from Table I who have bilateral disease and persistent cavity on the unoperated side, the corrected figures are recorded in Table Ia.

Sputum conversion related to size of cavity is shown in Table II.

Excluding patients from Table II who have bilateral disease and persistent cavity on the unoperated side, the corrected figures are recorded in Table IIa.

The x-ray films illustrate a patient with moderately advanced tuberculosis with cavitation in the left apex. Figure 13 shows the

TABLE I

Interval After Second Stage	No. of Patients	Sputum Conversions	Per cent
Over 1 year	3	3	100
6 to 12 months	17	13	76
3 to 6 months	22*	11	50

*One fatality not included.

TABLE Ia

Interval After Second Stage	No. of Patients	Sputum Conversions	Per cent
Over 1 year	3	3	100
6 to 12 months	15	13	87
3 to 6 months	20	11	55

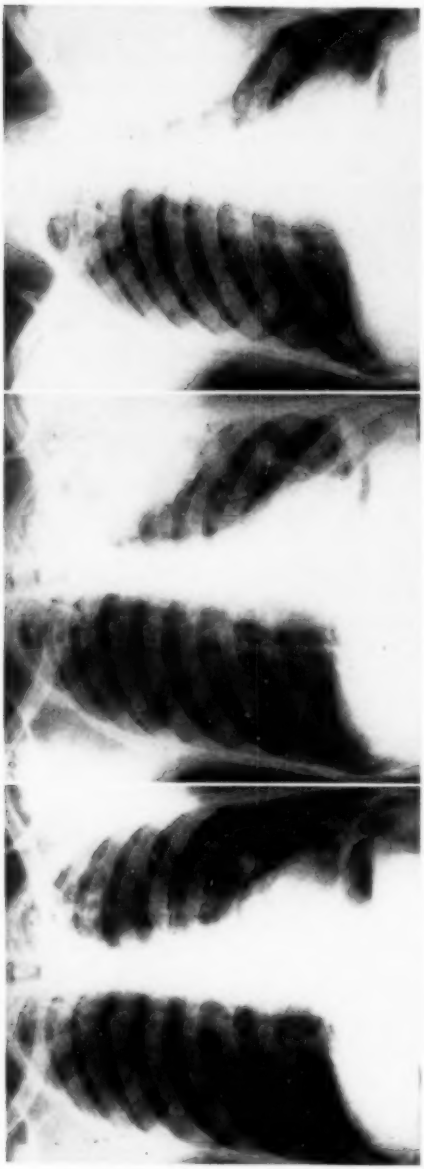

FIGURE 15

FIGURE 14

FIGURE 13

cavitary disease before operation. Figure 14 shows the x-ray appearance between the two operative stages. The extent of the collapse is nicely outlined by the fluid and the lucite spheres in the extraperiosteal space. Figure 15 shows the condition several months after operation at which time the sputum is negative.

Discussion

The plan of operation presented overcomes several of the undesirable features of modern multistage thoracoplasty. With the first operative stage, the entire desired collapse is obtained. Furthermore, our experience has shown that better collapse is obtained than when an identical pattern of rib resection is done in multiple stages. For this reason, the operation has been extended to patients in whom only two stages would be needed by the ordinary method. A potential modification might involve leaving the transverse processes and the first rib intact at the second stage. There is no paradox following the first stage. If the time interval between stages is adequate, there is insignificant paradox after the second stage. Conversion of sputum has been more rapid and has been accomplished in several instances between stages. Referring physicians in sanatoria have noted that patients complete their surgical program in better condition. There is, of course, a considerable reduction in the expense of the shortened surgical program.

The dangers of plombage are infection, erosion through pressure necrosis, and migration of the plombage material. These complications in extrapleural pneumonolysis and plombage are in part due to the deficient circulation of the thin layer of tissue between the cavitary disease and the plombage. In extraperiosteal plombage

TABLE II

Size of Cavity	No. of Patients	Sputum Conversions	Per cent
Over 6 cm.	3	2	67
4 to 6 cm.	17	10	59
Under 4 cm.	23*	17	74

*One fatality not included.

TABLE IIa

Size of Cavity	No. of Patients	Sputum Conversions	Per cent
Over 6 cm.	3	2	67
4 to 6 cm.	14	10	71
Under 4 cm.	22	17	77

an additional layer of tissue, consisting of the intercostal muscle and the periosteum having the excellent blood supply of the intercostal vessels, is interposed between the cavitary disease and the plombage. By removal of the plombage at the second stage, these dangers are eliminated. However, should some complication make a second stage inadvisable, an indefinite delay would entail little additional risk.

Postoperative care has been generally simplified. Even patients with large amounts of sputum are able to effetcively raise the sputum because there is a rigid chest wall to cough against. Generally, by the time of the second stage, the sputum is decreased in quantity, it is less tenacious and raising is no problem. Extraperiosteal fluid accumulation depends upon thorough hemostasis and lavage of the space before introduction of the plombage. On the average, less than one aspiration has been needed, although in several cases, a great number has been required. Pleural fluid formation has occurred only when the pleura has been torn. This may require several intrapleural aspirations; recently we have preferred intrapleural catheter drainage for 24 to 48 hours. Bacteriological study of all aspirated fluids in the first 45 cases was negative for pyogenic and acid fast organisms with one exception. Gauze surrounded by polyethelene sheeting was used as plombage only in the first three cases. Excessive fluid accumulated in all three, and one became infected. In a few instances, migration of the lucite balls has occurred and only between ribs. This has been overcome by using larger balls in patients with large interspaces.

CONCLUSIONS

A two-stage thoracoplasty has been devised using temporary extraperiosteal plombage. It has been found safe and effective even in patients up to 64 years of age and in those with extensive pulmonary tuberculosis.

CONCLUSIONES

Se ha inventado una toracoplastia a dos tiempos en la que se emplea un plombaje extraperióstico transitorio. Se ha demostrado que no tiene peligro y que es eficaz aún en pacientes hasta de 64 años de edad y en aquellos que tienen tuberculosis pulmonar extensa.

Preliminary Report of Clinical Experience with p-Aminosalicylic Acid*

NICHOLAS H. DeJANNEY, M.D., F.C.C.P., JOHN COX, M.D. and ELLEN GRINDELL-BALCHUM, M.D.
Detroit, Michigan

Clinical evaluation of p-aminosalicylic acid (P.A.S.), as a bacteriostatic agent in tuberculosis, is still limited because of the small number of cases treated and the length of the follow-up period. However, the results of other workers with the drug and our own experience with patients treated at our hospital have been sufficiently promising to justify the conclusion that P.A.S. is an effective agent in the treatment of tuberculosis.

Bernheim's[1] work in this country with benzoic and salicylic acids indicated that these two acids caused an increase in oxygen consumption of human strains of the tubercle bacillus. He concluded that these two acids were actively metabolized by the organism. Reasoning that derivatives of benzoic acid might compete in this metabolic process, Lehmann, in Sweden, examined over 50 compounds derived from benzoic acid. He found several that were tuberculostatic but finally selected p-aminosalicylic acid (P.A.S.) as the most promising.[2]

P.A.S. is a white to tan crystalline powder. As the free acid it is only slightly soluble in water but is freely soluble in alkaline solution. It is unstable to heat, especially in solution form, and exposure to sunlight causes oxidation and darkening.

O'Connor[3] emphasizes that solutions of sodium p-aminosalicylate should be water clear, and that only mild alkalis such as sodium bicarbonate should be used to neutralize the acid. He maintains that excess of alkali causes the solution to darken, with consequent deterioration of its potency. This claim is denied by Whittet[4] and disregarded by the Swedish workers[5,6] who have used more highly colored P.A.S. as well as dark-colored sodium salt solutions. Dempsey and Logg[7] used sodium hydroxide rather than milder alkalis on P.A.S. to obtain their sodium salt solution with apparently equally good results.

Absorption of the drug is rapid and almost complete from the gastrointestinal tract. It is likewise rapidly excreted, 50 per cent or more being removed by the kidneys mainly unchanged, or as the 4-acetomide compound. It is no longer found in the urine

*From Herman Kiefer Hospital, Detroit, Michigan.

within 20 hours after discontinuing intake. The urinary concentration quickly reaches high levels, 400 mg. per cent or more in one hour. P.A.S. is also found in the sputum in concentration of from 1 to 5 mg. per cent, and apparently purulent sputum contains a higher concentration than mucus sputum.[8,9] Transitory urinary casts and transitory albuminuria have been observed but no investigator has noted permanent renal damage.

The free acid has a rather unpleasant acrid taste which is difficult to disguise, and may cause mild to severe gastric irritation. To overcome these drawbacks Lehmann used the acid in enteric coated tablets. Erdei,[10] Dempsey and Logg used the sodium salt solution, which, although bitter, is claimed to be not unpleasant; the bitterness being readily disguised with flavoring agents. Erdei[9] observed "no real toxic manifestations at daily doses of up to 25 gm.; but in a few instances nausea and even vomiting have set in, perhaps because the solution was given without sufficient dilution, or because it was not suitably flavored." He warns that "even small doses of aspirin inadvertently given may precipitate symptoms of severe salicylate poisoning."

The drug has been administered experimentally to animals by the oral, subcutaneous, intramuscular, intravenous and topical routes. In clinical practice only the oral and topical methods are employed. Under topical methods are included the instillation of the drug into sinus tracts and serous cavities as well as local application to the skin surface. If the drug is used by either of the other routes in effective therapeutic dosage it may cause tissue necrosis.[11] The early recommended dosage was 15 to 18 gm. daily in divided doses at four-hour intervals. Erdei and Snell gave 12 gm. daily with their first series of patients but thought that was too low. They believed the daily amount should be 20 gm. In a later report Erdei gave up to 25 gm. daily.

Lehmann's *in vitro* research revealed that P.A.S. added to the media inhibited the growth of the tubercle bacillus. Later he found that it was a highly effective agent in retarding the progress of experimental tuberculosis in mice and guinea pigs. This work was confirmed experimentally by Youmans,[12] Youmans, Youmans and Osborne,[13] Feldman, Karlson, Carr and Hinshaw[14] and others. On the other hand McClosky, Smith and Frias[15] after extensive research on the efficacy of P.A.S. in rabbits and guinea pigs infected with tuberculosis, concluded that the drug had at best but little therapeutic effect.

Lehmann irrigated tuberculous abscesses in humans with neutral 10 per cent sodium salt solution of P.A.S. with resultant healing within a few months. In 1946[16] he reported on 20 patients treated with oral P.A.S. on a daily dosage of 10 to 15 gm., given in five

divided doses. This treatment resulted in prompt diminution of fever, improvement in general condition, increased appetite, weight gain, higher red blood count and hemoglobin and decreased sedimentation rate. Alin and Difs,[17] Vallentin,[18] Erdei and Snell,[10] Dempsey and Logg[7] and others have checked and expanded Lehmann's work. They are in general agreement with the beneficial action of P.A.S. cited above, and have found that the drug inhibits to a varying degree the progression of pulmonary, meningeal, skin and intestinal tuberculosis. Closure of draining sinuses, healing of abscesses and improvement in empyemata were also observed. Dempsey apparently had marked success in the treatment of tuberculous empyema with a 5 per cent suspension of the free acid intrapleurally. Carstensen treated 22 cases of intestinal tuberculosis "usually with striking results." Lemming[19] treated a recalcitrant case of skin tuberculosis present for over 14 years. The lesion did not respond to 20 per cent P.A.S. ointment but showed remarkable healing with gauze wetted with neutral 10 per cent solution of P.A.S. Pfuetze and Pyle[20] report a dramatic recovery from tuberculous peritonitis with closure of an abdominal fecal fistula during four months of treatment with 10 to 12 gms. of P.A.S. daily.

That this drug may be effective against tuberculous meningitis is suggested by the concentration in the spinal fluid. In one case of Alin and Difs it was 40 to 60 per cent of that in the blood. Lehmann, as well as Youmans, feels that, as in streptomycin, 1 mg. per cent P.A.S. in blood or spinal fluid is tuberculostatic. Dye[21] has shown that a daily dosage of 10.8 gms. and above on a schedule of every three hours will usually maintain free P.A.S. levels of 1 mg. per cent after one week of therapy. This value is comparable with that produced by a daily streptomycin dosage of 1.0 gm. The spinal fluid levels will likewise be over 1 mg. per cent free P.A.S.

This new drug has also been proposed as a useful means of delaying emergence of streptomycin resistance. Recently Dunner[22] and his co-workers combined these two drugs in the treatment of 11 patients who had not received either drug previously. At the end of two months none of the patients showed resistant organisms. At the Seventh Streptomycin Conference of the Veterans Administration held at Denver, Colorado, April 1949, compiled tabulation revealed three out of 26 or 12 per cent of the patients on the combined drug therapy had resistant organisms at the end of two months and 42 per cent at the end of four months. In contrast, those patients receiving only 1.0 gm. of streptomycin daily developed resistance in 49 per cent of the cases at the end of two months and 73 per cent at the end of four months. Leh-

mann[23,24] has been unable to demonstrate resistance developing to P.A.S. However, Dunner found some evidence of development of resistance. The clinical course of too many of our patients suggests a loss of sensitivity to P.A.S. on the part of the tubercle bacillus for us to discount the possibility of the development of resistance.

The present series comprises 42 patients, 40 with pulmonary tuberculosis and two with tuberculous meningitis. Among the pulmonary cases there were five who also had endobronchial lesions which failed to respond to prolonged streptomycin therapy.

The material used in this study was Pamisyl.* It was given in tablet form, except for a short period when the powder was used. In the early part of the study an attempt was made to maintain a dosage of 15 gm. daily from the beginning of treatment. On this regimen almost all the patients tolerated the drug poorly. Therefore, the amount was reduced to from 9.6 to 10.5 gm. daily, administered in five divided doses, q 4 hours, omitting the 4:00 a.m. dose. A further modification was made by starting with 6 gm. daily, gradually increasing the amount until the desired dosage was attained in six or seven days. Few patients had much difficulty with this plan and this is the regimen followed to the present. Where clinical and x-ray improvement occurred and were maintained the drug was usually continued for 90 to 120 days. The shortest effective course in this series was 30 and the longest 150 days.

The patients ranged in weight from 85 to 205 pounds, the majority weighing from 115 to 130 pounds. The effectiveness of the drug in the dosage given apparently had no relationship to the weight of the patient. The result was as good in the patient weighing 205 as in the one weighing 85 pounds. The age distribution was from 17 to 58, 50 per cent falling in the 20 to 30 age group.

Although many reports state that toxic manifestations have been rare, there were many encountered in this study, as shown in Table I. Of the 42 patients only 15, or 35.7 per cent, showed no evidence of toxicity. Of the 27 who had some untoward reaction, four had symptoms severe enough to require discontinuance of the drug. However, all four had been receiving 14 to 15 gm. daily. Three were able to resume therapy on a dosage of 9.9 gm. daily. Of these three, two exhibited no adverse symptoms and one only mild symptoms during the second course.

The most common complaints were anorexia, nausea, diarrhea, weight loss, and vomiting, all usually intermittent. There was no

*Pamisyl (R) registered trade mark of Park, Davis and Company for Para-Aminosalicylic Acid and supplied through their courtesy for this study.

tinnitus or vertigo, and no evidence of hematopoietic, renal, or hepatic damage.

Counterbalancing the toxic manifestations, definite symptomatic improvement was observed in 22 of the 37 patients who had any symptoms when P.A.S. was started. These symptomatic benefits are tabulated in Table II, and consisted of an improved sense of well-being, reduction of fever, decrease in cough and in amount of sputum. Some showed improved appetite rather than anorexia. In almost all cases symptomatic benefits appeared within the first month of treatment. Of the 20 tabulated as showing no symptomatic improvement, five were asymptomatic before therapy. Most of the 15 who did not show improvement of symptoms were far advanced with a hopeless prognosis.

The type and extent of disease are shown by Tables III and IV. Since the drug was relatively unappraised clinically when this series was begun, it was not used on cases that might be expected to respond favorably to streptomycin. Its use was limited to patients with far advanced disease, all of whom, except five, had

TABLE I

TOXIC MANIFESTATIONS*

During PAS (Pamisyl) Therapy

Severity of Symptoms	Nausea	Vomiting	Diarrhea	Anorexia	Weight Loss
Insufficient to Discontinue or Reduce	11	6	13	10	8
Sufficient to Reduce	5	4	4	2	1
Sufficient to Discontinue	1	2	1	1	1
TOTAL	17	12	18	13	10

*15 patients had no symptoms of toxicity during therapy.

TABLE II

SYMPTOMATIC BENEFIT*

During Therapy with Pamisyl

	Temperature	Cough	Appetite	Well Being	Sputum Quantity
First Week	8	2	3	7	1
First Month	2	5		9	2
After First Month			1	1	
TOTAL	10	7	4	17	3

*20 had no symptomatic benefit, but of these 5 had no symptoms before PAS therapy was begun.

already been treated with three to seven months of streptomycin and had reached a static condition or were getting worse. Of the 37 who received streptomycin 17 were known to be resistant to amounts ranging from 100 to 500 or more micrograms of streptomycin. There were 23 patients with predominantly exudative disease, 10 with mixed, seven with productive disease, and two with tuberculous meningitis without pulmonary lesions at the time of treatment. Thirty-six had bilateral and four unilateral disease. Of the latter one had had pneumonectomy. The disease was far-advanced in 34 and in only six was it moderately advanced.

The degree of cavitation is illustrated by Table IV. There was unilateral excavation in 24 cases and bilateral in 10. Only six had no demonstrable cavity. The total diameter of all cavities present was from 2 cms. or less in eight cases (one of these was the pneumonectomy case) to 6 cms. or more in eight cases. The greatest cavitation was seen in a white male patient, aged 42 years, who had a 10 cm. cavity above another one 5 cms. in diameter. This patient failed to derive any benefit from P.A.S. therapy and the drug was discontinued after 30 days.

An analysis of the duration of treatment reveals that at the present time 13 patients were treated for six weeks or less; the other 29 for more than six weeks (seven weeks to five months). Of the former, five are still under treatment and eight have had

TABLE III

EXTENT OF DISEASE (Infiltration)
Treated by Pamisyl

	Mod. Adv.	Far Adv.	Total		
Exudative	4	19	23	Unilateral	4
Mixed	1	9	10	Bilateral	36
Productive	1	6	7		
TOTAL	6	34	40		40

TABLE IV

EXTENT OF DISEASE (Cavity)
Treated by Pamisyl

No Cavity	Unilateral	Bilateral	Total
6	24	10	40

Total Diameter of Cavities

2 cms. or less	2 to 4 cms.	4 to 6 cms.	6 cms. and over	Total
8	8	10	8	34

therapy discontinued, either because of disease recognized as hopeless or because improvement was believed satisfactory. No case has been considered that had less than 30 days of treatment.

An attempt has been made in Table V to correlate the duration of treatment with improvement observed in the types of tuberculosis. Thus, instead of 40 cases we consider 47 "lesions": two of meningitis, 40 of pulmonary disease and five endobronchial lesions. Of those receiving P.A.S. less than six weeks, seven (53.8 per cent) showed no change or were worse, five (38.4 per cent) showed improvement directly attributable to P.A.S. and one showed improvement which could not be credited solely to P.A.S. because of associated treatment. Of the lesions treated with P.A.S. for more than six weeks, six (17.6 per cent) showed no change or were worse, 23 (67.6 per cent) showed improvement directly attributable to the drug and five showed improvement which could not be credited solely to P.A.S. because of other concurrent treatment. Thus, of 47 "lesions" treated 28 or 59.5 per cent, showed definite improvement by roentgenologic evidence attributable to P.A.S. therapy, while six (12.8 per cent) showed definite improvement wherein P.A.S. played a partial role along with other therapeutic measures.

TABLE V

DURATION OF THERAPY RELATED TO EFFECT ON LESIONS*

	No change or worse	Improvement attributable to PAS	Improvement indeterminate	Total
6 weeks or less	7	5	1	13
Over 6 weeks	6	23	5	34
TOTAL	13	28	6	47

*The difference in the total of this chart is due to inclusion of two patients with tuberculous meningitis and five with endobronchial lesions who also had pulmonary lesions.

TABLE VI

EFFECT OF PAS (PAMISYL) ON DISEASE

	Pulmonary Tuberculosis	Endobronchial Tuberculosis	Tuberculous Meningitis
Slight Improvement	3		
Moderate Improvement	15		
Marked Improvement	9	5	2
No change or worse	13		
TOTAL	40	5	2

Of 40 patients with pulmonary lesions, 27 showed significant x-ray improvement (Table VI) while 13 showed no change or were worse roentgenologically. Six of those who showed clearing of infiltrations and decrease in size of cavity fall into the category of improvement not directly attributable to P.A.S. because of concurrent treatment; the remaining 21 unquestionably represent a response to P.A.S., either because it was given without other treatment or because the associated treatment had been a failure during a long period of trial before P.A.S. was added. Bronchoscopy showed subsidence of edema and reddening and healing of endobronchial ulcers in the five patients with proved endobronchial disease after one month of P.A.S. treatment. In the two patients with meningitis marked P.A.S. benefit was observed. Both were given the drug during a relapse following six months of streptomycin administration. It may be mentioned here that our experience in the past with relapse cases of tuberculous meningitis has been most disappointing when streptomycin alone has been used a second time. All such cases have died. The two relapse cases of this study were at first put back on streptomycin. When they showed no response to this drug P.A.S. was added to their therapy. Within two weeks both showed marked clinical and spinal fluid improvement. One relapsed again when our supply of the drug ran out after 84 days of treatment. When a new supply was obtained this patient already had such intractable vomiting that the medication could not be retained. The other patient, who had no break in the course of her therapy, is now asymptomatic and shows steady return of spinal fluid composition toward normal, one month after discontinuance of a 144 day course of combined P.A.S. and streptomycin.*

The following case reports have been selected as being illustrative of those that showed definite objective improvement on P.A.S. therapy:

Case 1: J.A., a white female, age 17 years, was first admitted to another sanatorium in 1946 with history of hemoptysis during the previous three months. X-ray film showed evidence of dense infiltration in the apex and first interspace of the right lung. Bronchoscopy in October and December, 1947 revealed no abnormality. Right phrenic nerve was crushed December 12, 1946. Right pneumothorax was attempted but abandoned because

*Subsequent to this study another patient, a colored female aged five years, who had done well at first on streptomycin, had a relapse and became stuporous. Streptomycin was discontinued and treatment with P.A.S. was instituted. The sensorium showed a remarkably early clearing. Seventy-two hours later the patient was out of her stuporous state and observing activities going on about her. After three more days she was sitting up in bed. Treatment was started with 4.5 gm. of P.A.S. on the first day. The tablets were crushed to powder and given per intranasal catheter because she was unable to swallow. The amount was increased by 1.5 gm. daily until 10.5 gm. per day was reached at which dosage it was maintained.

it was unsuccessful. From January 16 to February 22, 1948 she received 42 gm. of streptomycin. From October 1946 to July 1948 the sputum was negative on only eight occasions. She was transferred to Herman Kiefer Hospital for surgery in July 1948. An x-ray film at this time revealed an area of increased density in the right inner lung field extending from the root into the apical region (Fig. 1a). Small scattered areas of productive infiltration were present in the upper third. The left lung was clear. The density on the right suggested atelectasis of the upper lobe. Right upper lobe resection was decided upon. However, when surgery was done on August 30, 1948 instead of right upper lobe resection it was necessary to do pneumonectomy because the disease process was found to be present in the middle and lower lobes as well as the upper. The operation was carried out in the chest-down position. At completion of surgery she was bronchoscoped and considerable muco-purulent and bloody secretions were removed. She left the operating room in good condition. The path-

FIGURE 1a FIGURE 1b

CASE 1 (Figure 1a): Pre-operative film, August 28, 1948.
(Figure 1b): September 9, 1948. Shows spread to left.

FIGURE 1c FIGURE 1d

CASE 1 (Figure 1c): October 20, 1948. Only slight clearing after two months of streptomycin.—(Figure 1d): January 3, 1949. Marked clearing of infiltration after six weeks of P.A.S.

FIGURE 2a FIGURE 2b FIGURE 2c

CASE 2 (Figure 1a): September 27, 1948, Far advanced tuberculosis with cavity at right hilum.—(Figure 2b): October 16, 1948, Increase of infiltration at right base, cavity larger.—(Figure 2c): November 22, 1948, One month after P.A.S. started. Cavity at right hilum no longer visible.

ologist reported that the upper and middle lobes failed to expand and consisted of dense fibrous tissue. A 3 x 4 cm. cavity was located in the lateral portion of the upper lobe, small cavities were present in the middle portion. Numerous nodules were in the upper and middle lobes varying in size up to 3 cms. Many of these showed central areas of softening and caseation. The right upper lobe bronchus was narrowed to 50 per cent of its normal size. The pathological diagnosis was productive tuberculosis with cavitation, pulmonary fibrosis and tuberculous bronchiectasis. At operation she was started on streptomycin, ½ gm. intramuscularly, and also received 1 gm. of streptomycin intrapleurally every other day for four doses. X-ray film inspection on September 9, 1948 revealed evidence of disease in the left lung (Fig. 1b). In October, almost two months after streptomycin was started, there was practically no change in appearance of this disease (Fig. 1c). P.A.S. was started November 21, 1948, with a daily dosage of 7.5 gm. She tolerated the drug well and an x-ray film taken early in January, 1949 showed a marked clearing of the infiltration (Fig. 1d).

Case 2: M.B., a white female of 28 years, was admitted January 17, 1948 complaining of fatigue, insomnia, anoxeria, cough, bilateral chest pain of pleuritic nature, night sweats and weight loss of 20 pounds during the past four months. X-ray film inspection on admission revealed evidence of extensive disease of exudative type involving areas throughout nearly all of both lungs. Evidence of beginning cavitation was seen on the right side. Her sputum contained tubercle bacilli. She was also found to have chronic cholecystitis and cholelithiasis. Streptomycin, ½ gm. daily was begun January, 1948. She improved both clinically and roentgenologically. On October 13, 1948 cholecystectomy was performed with uneventful recovery. Streptomycin was discontinued in April, 1948 but begun again two months later during the period of gall bladder surgery. It was finally discontinued in September, 1948 (Fig. 2a). During the second course of streptomycin the patient did not exhibit steady improvement of her pulmonary disease. In July the cavities on the right were larger. Then they decreased in size and the infiltration in both lungs showed some clearing. But in October the roentgenogram showed a definite increase of infiltrations at the base of the right lung and the cavity near the root of this lung was larger and more distinct (Fig. 2b). No change was seen in the left lung. It was evident when streptomycin was discontinued that it was no longer controlling the disease. In May, 1948 the laboratory reported that the tubercle bacilli of this patient were slightly resistant to 100 units of streptomycin and sensitive to 500 units. But in October, 1948 the tubercle bacilli were definitely resistant to 100 units of streptomycin and partially resistant to 500 units. Treatment with p-aminosalicylic acid was started October 21, 1948. A roentgenogram one month later showed marked clearing of the infiltrations in the right lung and the cavity was not visible. The left lung also showed a decrease in the density of the infiltration (Fig. 2c). P.A.S. was discontinued December 3, 1948. One month after discontinuance improvement continued to take place. The former cavity on the right was still not visible.

Case 3: B.K., a white female of 23 years, was admitted May 26, 1947 with history of 28 pounds weight loss during the past two and one-half years. Dry cough had been present for about eight months. She had consulted her family doctor who referred her to Herman Kiefer Hospital after a

chest x-ray film was taken. She appeared chronically ill. Her sputum was positive and x-ray film inspection revealed predominantly productive infiltrations throughout nearly the entire right lung with several areas of rarefaction suggesting cavities in the upper one third. On the left there were infiltrations throughout the upper half with several areas of rarefaction resembling cavities, the largest measured 3 cms. in diameter (Fig. 3a).

Pneumothorax was unsuccessful on both the right and left sides. Pneumoperitoneum was induced in August, 1947. It was discontinued as ineffectual in July, 1948 when $\frac{1}{2}$ gm. of streptomycin daily was begun. Three months later no response could be seen: in fact, the infiltrations on the left appeared more dense and the cavity was larger (Fig. 3b). On October 29, 1948 P.A.S. was added, 10.5 gm. daily, to the streptomycin therapy. One month later there was marked absorption of the infiltrations; the cavity was a great deal smaller and indistinct. Four months after P.A.S. therapy was begun the rarefaction on the right was much smaller; on the left the infiltrations were more productive and no definite cavity could be seen (Fig. 3c). Pneumoperitoneum was reinstituted on March 4, 1949 with the purpose of maintaining the improvement. X-ray film inspection on March 28, 1949 showed no evidence of cavity in either lung.

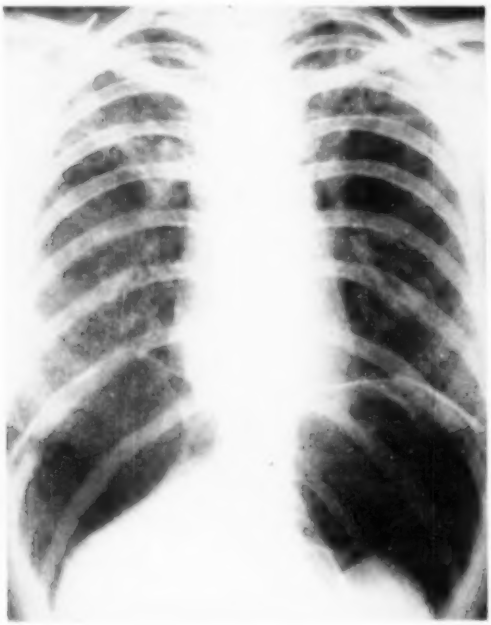

FIGURE 3a

CASE 3: July 16, 1948. A thin-walled 2 cm. cavity is at outer zone of right second interspace. On the left there are dense infiltrations in upper third with a 4 cm. cavity at the first interspace.

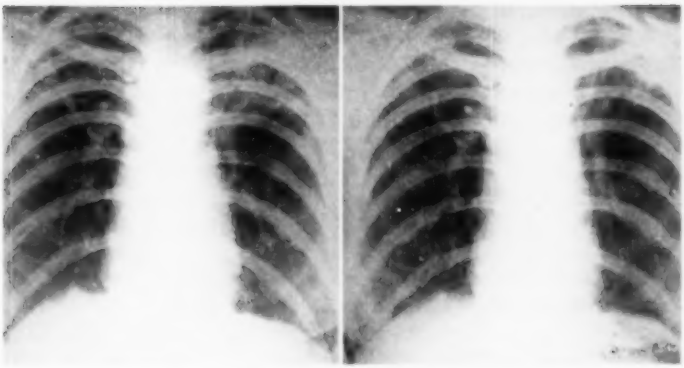

FIGURE 3b FIGURE 3c

CASE 3 (Figure 3b): October 21, 1948. Three months after streptomycin. The cavity on the right is smaller, but on the left the cavity is larger and the infiltrations have increased in density.—(Figure 3c): February 28, 1949. Four months after P.A.S. added to therapy. On the right the rarefactions are smaller and less distinct. No definite cavity. On the left the infiltrations are more productive and cavity is no longer visible.

SUMMARY

Although European researchers generally state that few toxic reactions, if any, result from administration of P.A.S., and that it should be given in greater dosage than 15 gm. daily, our experience has been different. In this study 64.3 per cent of the patients had evidence of some degree of toxicity. Fifteen grams per day has been more than our patients, except for a very few, could tolerate when given as the free acid. There was fairly god tolerance on a schedule of 9.6 to 10.5 grams per day and this dosage was found to be therapeutically effective. On the other hand 22 cases (52.4 per cent) showed symptomatic benefit. Of the remainder who exhibited no symptomatic improvement 11.9 per cent were asymptomatic before P.A.S. was given. Perhaps the greatest difference in the drug as we employed it and as used in Europe is that ours was the uncoated tablet of the free acid whereas in Great Britain and on the Continent the investigators used the sodium salt solution or enteric coated tablets of the acid.

We wish to stress that in this series P.A.S. was given a most severe test. Eighty-eight per cent of the patients were streptomycin failures. Ninety per cent had bilateral disease. Cavities varied in size from less than 2 cms. to 15 cms. in diameter. Cavitation was present in all cases except six. Of the 40 patients with pulmonary tuberculosis 42.5 per cent had mixed or productive disease, and

definite clinical and x-ray improvement directly attributable to P.A.S. was seen in 27 or 67.5 per cent.

We also wish to emphasize the apparently great value of P.A.S. in endobronchial tuberculosis. Five patients with pulmonary disease also had endobronchial tuberculosis previously treated unsuccessfully with streptomycin; the lesions healed in all five of these cases.

Two patients with tuberculous meningitis suffered a relapse subsequent to six months of streptomycin therapy. Reinstitution of treatment with streptomycin appeared to be ineffective. With the addition of P.A.S. both had remission of their symptoms. The drugs have been discontinued for three months in one of these patients. The spinal fluid chemistry now approaches normal limits. All other patients with tuberculous meningitis who responded favorably but later relapsed, died when streptomycin alone was used.

Dunner has stated that resistance to P.A.S. develops in the tubercle bacillus. At least clinically we have evidence to uphold this conclusion. In some cases, after approximately four months of treatment with P.A.S., loss of its effect has been observed, as evidenced by increase of disease. It is highly questionable, therefore, whether one should seek to obtain the combined effect of streptomycin and P.A.S. routinely unless the two drugs are used for a short course, perhaps no longer than three months. It is desirable to have one drug in reserve in the event resistance develops to the other. When a patient is being prepared for surgery P.A.S. might be used preoperatively for two or three months. During surgery and postoperatively, especially in cases of resection, streptomycin alone, or P.A.S. combined with streptomycin, might be used advantageously for one or two months to obviate or control postoperative spreads.

In a number of patients it has been observed that the early good effect of P.A.S. was lost after approximately four months. Therefore, when collapse therapy is necessary in a patient receiving P.A.S. it should be instituted as early as the criteria for collapse therapy will permit, before loss of P.A.S. effect may develop.

CONCLUSIONS

1) P.A.S. is of decided value not only in the exudative type of tuberculosis but also (to a lesser degree) in the mixed and productive types.

2) We have found it highly effective in endobronchial tuberculosis.

3) It is highly valuable in the treatment of cases of tuberculous meningitis that relapse after a favorable response to streptomycin therapy. In our experience all relapse cases of tuberculous meningitis treated with streptomycin alone have died. The only

survivals have been those treated with combined streptomycin and P.A.S. or only with p-aminosalicylic acid.

4) Pulmonary tuberculosis which has failed to respond to streptomycin does not preclude the use of P.A.S. Of such cases in the present series 67.5 per cent showed improvement directly attributable to the latter drug.

5) Where collapse treatment is indicated it should be started early in the course of P.A.S. treatment, before the drug effect is lost.

RESUMEN

Aunque los investigadores europeos generalmente declaran que la administración del PAS ocasiona pocas reacciones tóxicas, o no causa toxicidad alguna, y que debe administrarse esta droga en mayores dosis que 15 Gm. al día, nuestra experiencia ha sido distinta. En el presente estudio el 64.3 por ciento de los pacientes exhibieron algún grado de toxicidad. Con muy pocas excepciones, nuestros pacientes no han podido tolerar 15 Gm. al día administrados en la forma del ácido libre. Se toleró bastante bien un plan terapéutico de 9.6 a 10.5 Gm. al día y se descubrió que esta dosis es eficaz. Veinte y dos casos (el 52.4 por ciento) manifestaron beneficio sintomático. Entre los otros, que no revelaron mejoría sintomática, el 11.9 por ciento ya estaban asintomáticos antes de la administración del PAS. Tal vez la mayor diferencia entre la forma en que empleamos la droga y la manera en que se usó en Europa fue que nosotros usamos el ácido libre en tabletas no revestidas, mientras que en la Gran Bretaña y en el Continente los investigadores emplearon la solución de la sal sódica o el ácido en tabletas de revestimiento entérico.

Queremos recalcar que, en esta serie, el PAS recibió una prueba muy severa. En el 88 por ciento de los pacientes ya había fracasado la estreptomicina. El noventa por ciento tenían enfermedad bilateral. El tamaño de las cavernas variaba de menos de 2 a 15 cm. de diámetro. Todos los casos, con la excepción de seis, tenían cavernas. De los 40 pacientes con tuberculosis pulmonar, el 42.5 por ciento tenían enfermedad mixta o productiva, y se observó una mejoría clínica y radiológica bien definida, atribuible directamente al PAS, en 27 (el 67.5 por ciento).

También queremos recalcar el gran valor que el PAS parece tener en el tratamiento de la tuberculosis endobronquial. Cinco pacientes con enfermedad pulmonar también tenían tuberculosis endobronquial previamente tratada sin éxito con estreptomicina; en todos los cinco casos se cicatrizaron las lesiones.

Dos pacientes con meningitis tuberculosa sufrieron recidivas subsiguientemente a seis meses de estreptomicinoterapia. El tratamiento de nuevo con estreptomicina pareció ser ineficaz, pero con

la adición del PAS ambos enfermos obtuvieron remisiones de sus síntomas. Ya se han descontinuado las drogas por tres meses en uno de esos pacientes. Los resultados del análisis del líquido céfalorraquídeo ya se aproximan a los límites normales. Todos los otros pacientes con meningitis tuberculosa, que primero respondieron favorablemente pero que más tarde sufrieron recidivas, murieron cuando se empleó la estreptomicina sola.

Dunner ha afirmado que el bacilo tuberculoso desarrolla resistencia al PAS. Clínicamente, por lo menos, tenemos pruebas que corroboran esa conclusión. En algunos casos, después de unos cuatro meses de tratamiento con PAS, se ha observado la pérdida de su eficacia, comprobada por la extensión de la enfermedad. Se duda, pues, que uno deba tratar de obtener el efecto combinado de la estreptomicina y el PAS rutinariamente, a menos que las dos drogas se empleen por una corta serie terapéutica, tal vez de menos de tres meses. Es deseable que se tenga una droga en reserva, en caso de que se desarrolle resistencia a la otra. Cuando se prepare un paciente para la intervención quirúrgica puede usarse el PAS preoperatoriamente por dos o tres meses. Durante la operación y en el período postoperatorio, especialmente en casos de resección, podría ser ventajoso usar, por uno o dos meses, la estreptomicina sola, o el PAS combinado con la estreptomicina, a fin de evitar o controlar extensiones postoperatorias.

Se ha observado en ciertos pacientes que el buen efecto inicial del PAS se perdió después de aproximadamente cuatro meses. Por consiguiente, cuando se indica la colapsoterapia en un paciente que recibe PAS, debe iniciarse esta terapia tan pronto como lo permita el criterio para su empleo, antes de que pueda perderse el efecto del PAS.

CONCLUSIONES

1) El PAS tiene un decidido valor no solamente en la tuberculosis de tipo exudativo sino también (en un grado menor) en los tipos mixtos y productivos.

2) Lo hemos encontrado altamente eficaz en la tuberculosis endobronquial.

3) Es muy valioso en el tratamiento de los casos de meningitis tuberculosa que sufren recidivas después de una respuesta favorable a la estreptomicinoterapia. En nuestra experiencia, han muerto todos los casos con recidivas de meningitis tuberculosa que fueron tratados exclusivamente con estreptomicina. Los únicos sobrevivientes han sido los que fueron tratados con estreptomicina y PAS combinados, o solamente con el ácido para-aminosalicílico.

4) La tuberculosis pulmonar que no ha respondido a la estreptomicina no contraindica el empleo del PAS. De tales casos en la presente serie, el 67.5 por ciento manifestaron mejoría atribuible

directamente a esta última droga.

5) Cuando se indica la colapsoterapia, debe comenzarse tempranamente en el curso del tratamiento con PAS, antes de que la droga haya perdido su efecto.

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Studies on the Behavior of Para-Aminosalicylic Acid in Tuberculous Pleural Effusions*

S. H. LAWRENCE, M.D. and NATHANIEL COMDEN, M.D.†
San Fernando, California

In 1944, Lehmann[1] in Sweden, introduced para-aminosalicylic acid (PAS) as a chemotherapeutic agent against the tubercle bacillus. Since that time many clinical and experimental investigations have been done. Alin and Hilander[2] studied the distribution of PAS in the tissues after oral administration by the fluorescent microscopy technique. Klyne and Newhouse[3] determined the level of PAS in blood and cerebrospinal fluid. Gilliard[4] and Sivriere[5] report its use in the treatment of tuberculous empyemas.

In the course of studies on the therapeutic effect of PAS in tuberculous empyema, we observed that the drug disappeared rapidly after injection into the pleural cavity. The fate of this PAS was further investigated.

Procedure: Ten patients with pleural fluid were studied. All were being treated for pulmonary tuberculosis. The effusions were complications of pneumothorax, and varied from clear, straw-colored fluid to thick, creamy pus. In each case, tubercle bacilli were cultured from the fluid.

Methods for the determination of PAS levels have been described by Alin and Difs,[6] Dickenson and Kelly,[7] Oberweger, et al.[8] Wilson and Armstrong,[9] and Way, et al.[10] The method described by Way, et al, was used in these experiments.

Three groups of experiments were performed as follows:

I. In 10 patients, one to three grams of PAS (5 per cent PAS in a 5 per cent solution of glucose in water) were introduced into the pleural cavity after as much fluid as possible had been removed. Thoracentesis was repeated one week later and negligible PAS levels were obtained.

Following this, examinations were done at shorter intervals. Three grams of PAS in 150 cc. of fluid were instilled into the pleural cavity as before and the position of the patient was changed to allow for adequate mixture of the PAS with the remaining pleural fluid. Then, with the needle still in place, a sample of

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†From the Veterans Administration Hospital, San Fernando, California.

the mixed pleural effusion was withdrawn for analysis. Thoracentesis was repeated after six, 24, and 36 hours and samples were again tested. The results are shown in Table I.

In order to ascertain whether this decrease in PAS level was due to absorption or whether it might be due to deterioration or inactivation by some constituent of the purulent exudate, fluid from two patients was incubated at 37 degrees centigrade with the 5 per cent solution of PAS, and daily PAS levels were run on the mixture. The results are shown in Table II. Although there was a decrease in the PAS level from day to day, the drop was not comparable to the rapid disappearance of PAS in vivo.

TABLE I

Fall of Intrapleural PAS Levels Following Intrapleural Administration of PAS (mg./100 cc.)

	Original PAS Level	PAS Level After 6 Hours	PAS Level After 24 Hours	PAS Level After 36 Hours
Case 1	330	100	28	1
Case 2	250	80	22	0

TABLE II

Showing Decrease in PAS Incubated with Pleural Fluid (mg./100 cc.)

	Level Immediately After PAS was Added	1st day	2nd day	3rd day	4th day	5th day
Case 1	>100	43	40	35	30	30
Case 2	>200	150	110	100	90	90

TABLE III

PAS Blood Levels After Intrapleural Administration (mg./100 cc.)

	Amount Intrapleural PAS Introduced	Blood Levels After Administering PAS				
		0 hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Case 1	1 gm.	0	.0	0.5	0.5	
Case 2	1 gm.	0	0.5	0.5	.0	
Case 3	1 gm.	0	1.0	1.0	0.5	
Case 1	3 gm.	0	7.0	7.0	7.0	9.0
Case 2	3 gm.	0	7.5	7.8	6.0	5.8
Case 3	3 gm.	0	4.8	6.8	9.3	5.8
Case 1	3 gm.	0	4.0	4.0	2.4	
Case 2	3 gm.	0	7.0	4.8	3.0	
Case 3	3 gm.	0	2.4	2.2	1.0	

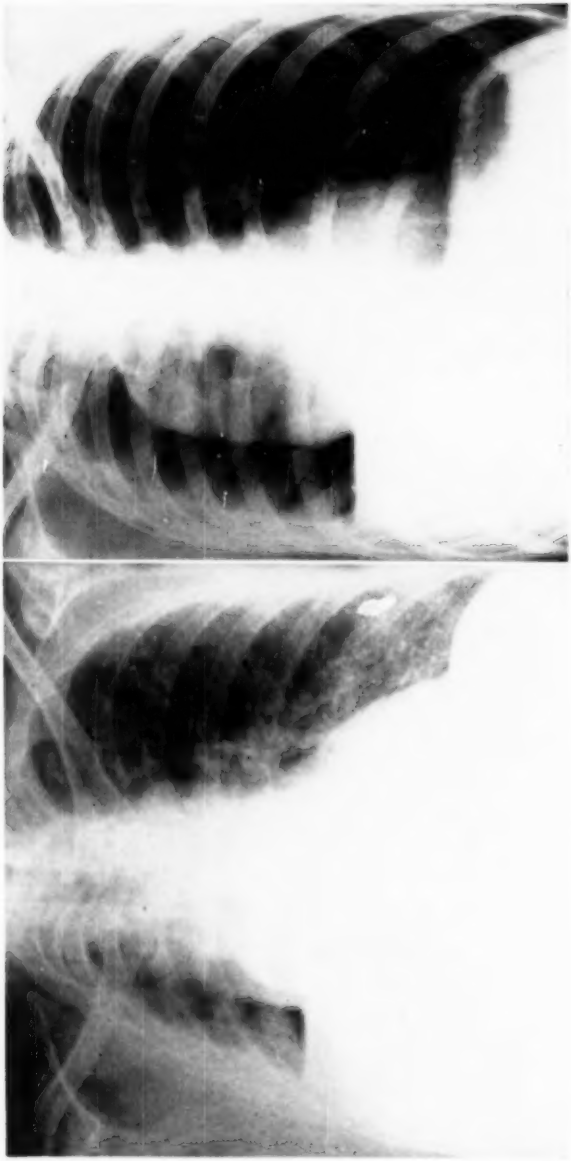

FIGURE 2

FIGURE 1

II. In three cases, the blood level was determined after instillation of PAS into the pleural cavity. In the first of these, only one gram was used, and the corresponding levels in the blood were so low that the accuracy of the determinations is questionable. However, during the later examinations, three grams were instilled. After one hour, a significant blood level occurred in all patients.

The x-ray reproductions of Cases 1 and 2, in whom a high PAS blood level was obtained are shown in Figures 1 and 2, and it will be noted that both visceral and parietal pleurae are markedly thickened, the parietal pleura measuring up to 1.5 cm.

III. In order to determine whether appreciable intrapleural levels of PAS could be obtained from oral dosage, chest fluid levels were run while the patients were maintained on 12 grams daily in four divided doses. These levels were all taken aproximately two hours after the last oral dose of PAS. The maximum levels were obtained after only a few days of oral therapy (Table IV).

TABLE IV

PAS Chest Fluid Levels After Oral Administration (mg./100 cc.)

	Days of Oral Therapy	Blood Level	Chest Fluid Level
Case 4	4	1.4	0.5
Case 5	4	1.8	1.4
Case 6	4	2.6	4.2
Case 7	100	1.5	2.4
Case 8	80	2.8	2.0
Case 9	92	3.2	2.0
Case 10	85	2.5	2.8

DISCUSSION

It is of interest to note that PAS was able to pass through the pleural barrier with surprising ease, both from the pleural fluid to the blood and after oral administration from the blood to the pleural fluid. Patients 1 and 2 (Table III) had markedly thickened pleura as is shown in their x-ray films (Figs. 1 and 2). Even in these cases a comparatively high blood level was present one hour after intrapleural administration of three grams of PAS.

In these 10 cases during the period of study, the PAS proved to be of limited value in the treatment of tuberculous pleural effsuions.

CONCLUSIONS

1) In the presence of tuberculous pleural effusions, PAS:
   a) when given intrapleurally, appears in the blood in significant amounts.

b) after oral administration it may be recovered from the pleural fluid in significant amounts.

2) These findings were observed in the presence of either serous or purulent exudates and with thickened as well as thin pleural membranes.

The authors wish to express their gratitude to Mr. Harold C. Haymond and Mr. George C. Kidd for their technical assistance in the PAS determinations.

CONCLUSIONES

1) En presencia de derrames pleurales el PAS:

a) Cuando se inyecta en la pleura aparece en la sangre en proporciones importantes.

b) Cuando se da oralmente puede encontrarse en el liquido pleural en proporciones importantes.

2) Estos hallazgos se observaron ya fuese el liquido seroso o purulento y con pleuras delgadas o engrosadas.

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Aerosols II
The Role of Particle Size in Inhalation Therapy by Atomization and by Penicillin Dusts*

HAROLD A. ABRAMSON, M.D., F.C.C.P.
New York, New York

The renaissance of aerosol therapy of the lungs and bronchi developed by war research, has led to renewed interest not only in nebulizers of the classical type in which the particle size distribution is determined by the baffling out of the larger droplets but also in atmoizers and particulate or dust aerosols for therapy of the respiratory tract.[1] It becomes of importance therefore, to determine the scientific basis for the use of atomizers and dusts in the therapy of the lungs. Therapeutic evaluations must at present be based not only upon clinical evidence which often is faulty but also upon physical evidence, that is, the probable distribution of the aerosol in particles of various sizes within the lungs themselves. This report deals with the particle size distributions of a commercial atomizer, the DeVilbiss No. 251 atomizer and three commercially available penicillin dusts, the particle sizes of which have been measured. The therapeutic possibilities of atomization and of penicillin dust therapy will be discussed from the point of view of the physical distribution of the atomized droplets and dust particles within the bronchi and the lungs. It will be shown that, if the particle size is too large to begin with (and in certain instances to be discussed in this paper this is true), this constitutes an *a priori* evidence that claims that the particles produce changes within the lungs must be modified or discarded.

Method

The particle size distribution of the droplets of atomized liquids and of particulate dust is a difficult problem to solve. We have been particularly fortunate, therefore, in having the collaboration of Professor H. G. Houghton of Cambridge, Massachusetts who not only made some of these measurements (DeVilbiss No. 251 and Penicillin Dust "X") but also aided in the evaluation of the data. Without his advice much of the value of this communication would be lost.

*From the 1st Medical Service and the Laboratories of The Mount Sinai Hospital, New York City.

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In general, the microscope was found useful with particles in the size range to be discussed. This is in contradistinction to the nature of the problem encountered with small rapidly evaporating droplets usually encountered in nebulized mists where a falling-drop method was previously required. Thus, during the war when it was necessary for the Chemical Corps to standardize nebulizers prior to the introduction of aerosol therapy in the field, the Biological Laboratory at Cold Spring Harbor was asked to develop a method of measuring particle size distribution in penicillin aerosols. This has been discussed elsewhere.[2,3] The irregularity of measurement encountered, particularly in the larger atomized drops discussed in Table I, would, of course, decrease if an increase of the total number of drops were to be made. However, irregularities shown in Table I, as well as in the other Tables, do not diminish the significance of the general trend of the particle size distributions of these droplets. Thus, at a pressure of five pounds per square inch (DeVilbiss No. 251) measurements of the droplets were made down to about a quarter of a micron in radius. As the

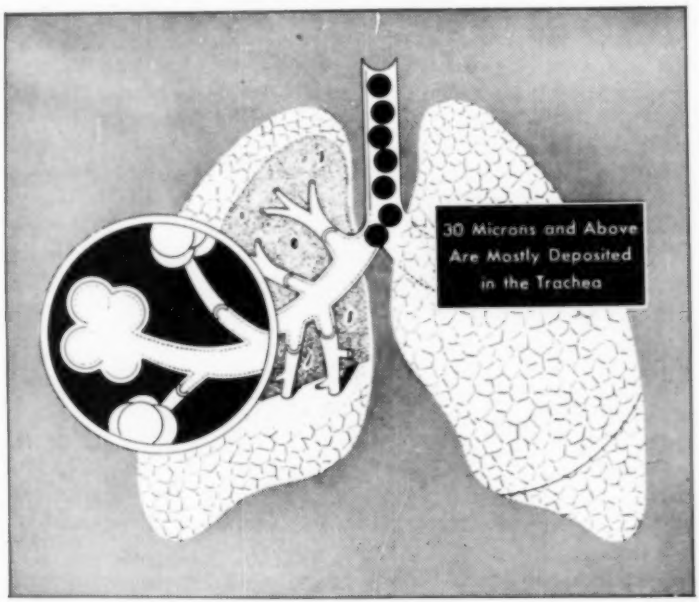

FIGURE 1: Particles above 30 u in radius are mainly trapped in the trachea. This occurs with most atomizers and is probably the main mechanism involved in mucosography (Fariñas). Atomization therapy will be of use in the treatment of the larger bronchial tubes and of mustard gas lesions of the trachea and bronchi.

pressure in the atomizer is increased however, the number of small droplets increases and the number of large droplets decreases. In order to prevent evaporation of the small drops, Houghton employed an aqueous solution of calcium chloride which was sprayed with its vapor-pressure adjusted to the ambient relative humidity and in equilibrium with it. In all cases this turned out to be an approximately 20 per cent solution of calcium chloride. This solution has a surface tension of about 81 dynes per centimeter, a viscosity of about 0.02 poises and a density of about 1.18. Although we are primarily interested here in the properties of penicillin and similar antibiotic solutions, this calcium chloride solution should not differ enough to affect appreciably the effective drop-size distribution with other solutions, in view of the fact that fairly concentrated solutions of penicillin, streptomycin, vitamin C, and other substances are used in the therapy of the lungs. Data on the effect of these solutions when they are atomized in concentrated form are not presently available. The writer however, has atomized a 5 per cent solution of sodium iodide into the larynx anesthetized with pontocaine without any cough or gagging.

The measurement of the penicillin dusts was made with a mi-

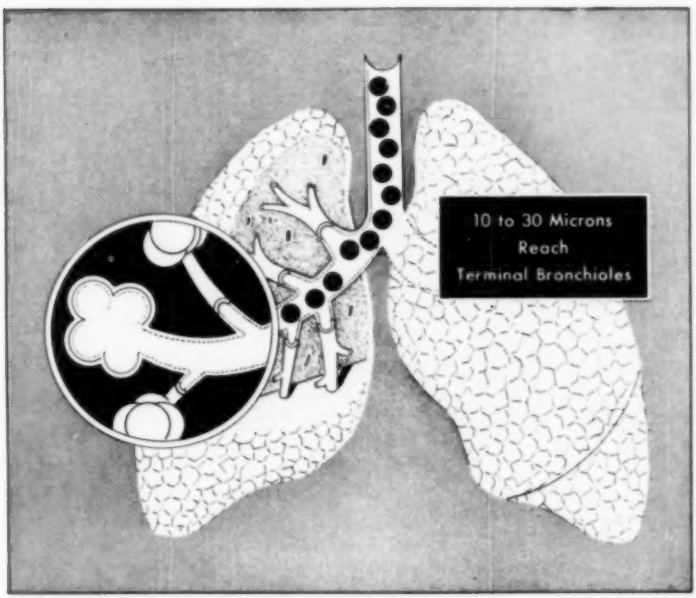

FIGURE 2: With particles ranging down to 10 u in radius, distribution occurs to the terminal bronchioles.

croscope using the largest diameter of the particle as the actual diameter. This introduces the error of dealing with an equivalent radius rather than with the actual radius assuming a shape, therefore, which the particle in reality does not possess. The quantitative significance of the data is therefore, somewhat lessened. This error however, is present in all of the measurements and in general, will tend to cancel out in a comparison of the type to be made. Further, it is better to have a fairly accurate semi-quantitative picture rather than no picture at all. The data are sufficiently quantitative to give a fairly good idea of dose distribution of penicillin and other medicinal dusts so that therapeutic potentiality is brought into a consistent pattern with what is known of absorption of dusts, in general. In Dust "X," the measurements were made by dispersing the powder in a volatile hydrocarbon to avoid agglutination. This was done because Dust "X" has particularly large particles when one considers the therapeutic claims made by the manufacturer. A sample of the suspension was placed on a microscope slide and the hydrocarbon allowed to evaporate. Observations were made with a conventional microscope with magnification of 500 times, which is about the greatest magnification which can be used for particle size distribution of the type en-

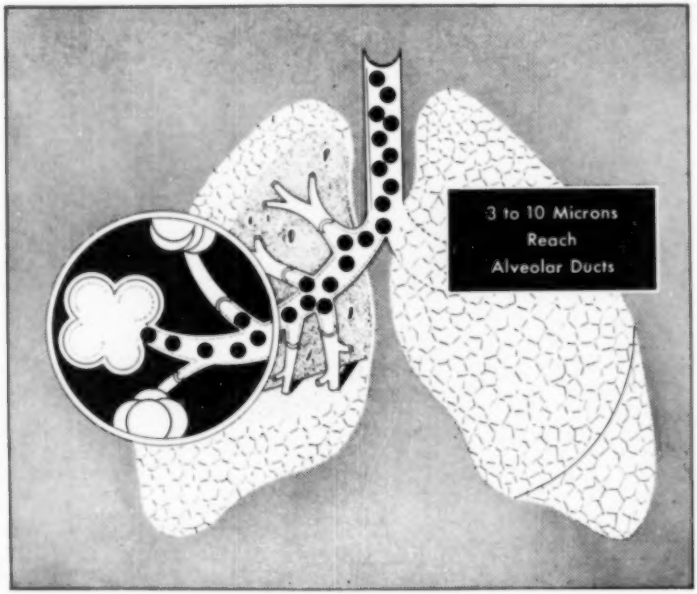

FIGURE 3: Particles 3 u to 10 u reach alveolar ducts.

countered. The error introduced by using only one projection might make the estimate of diameter somewhat large. In the case of Penicillin "X," measurements were made on three separate samples of the powder. The agreement between the samples was very good up to 35 microns and therefore the particle size distribution in "X" in the lower range is fairly accurate. Particular stress was placed upon Sample "X" because of the great number of large particles found in this powder. There was considerable divergence in the number and size of the particles larger than 35 microns. This variation may be partly due to chance since only a few large particles were measured in comparison with the smaller particles. However, we are more interested in the details of the distribution of the smaller particles compared with the larger ones in the given sample, since it is these samples which presumably reach the recesses of the lungs and are responsible for therapeutic results in the case of lung infections. Visual observations indicated unequivocally that the large particles in Penicillin "X" were not the result of clumping but actually constituted the makeup of the powder. Clumping of smaller particles was immediately recognizable. Penicillin dust manufactured by Schenley as well as penicillin

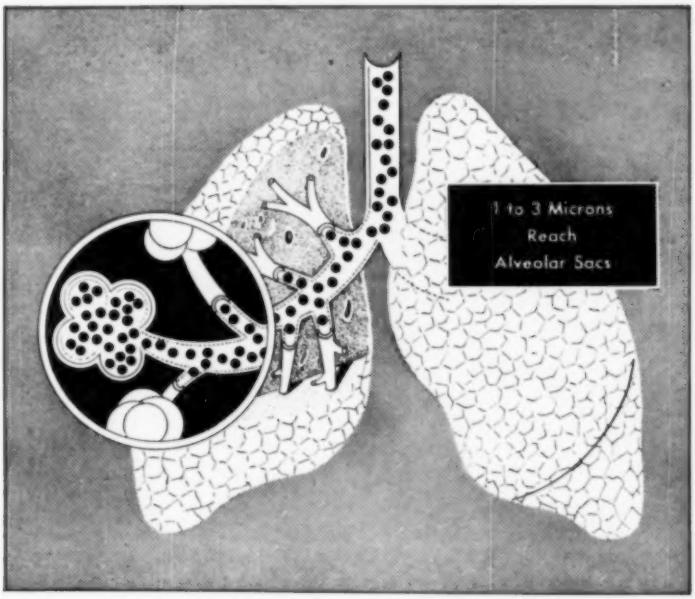

FIGURE 4: Particles below 3 u in radius reach the alveolar sacs. But not all particles are deposited to the same extent.

dust manufactured by Lederle was studied by direct microscopic observation. As yet, no method has been devised whereby particles of different sizes can be breathed in and their distribution within the lungs themselves be directly ascertained. However, we have both mathematical and practical data from the theory of Findeisen,[4] the researches of Fariñas,[3] and of Van Wigh and Patterson[7] who have given us some insight in the way that particles, especially smaller ones, may behave in the complicated labyrinthine structures of the lungs. According to the theoretical work of Findeisen (Figure 1), particles of 30 micra in radius are mainly trapped in the trachea. This occurs with ordinary atomizers and must be distinguished as probably the main mechanism involved in mucosography developed by Fariñas. It is assumed of course, that the particles are at the first part of the trachea to begin with. It should be recalled that in any discussion dealing with the distribution of large particles that if those of this size travel through the nose or through the mouth and pharynx, many of them will be trapped in the nasal passages and in the pharyngeal passages

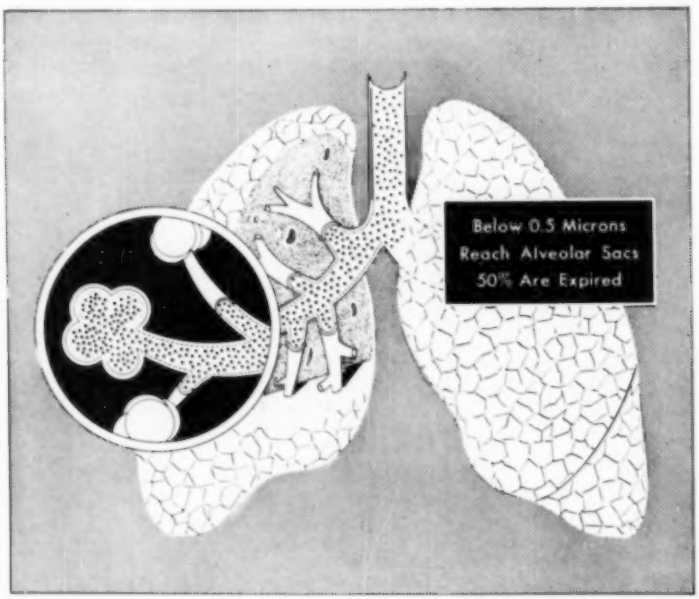

FIGURE 5: About 50 per cent of the particles 0.5 in radius and below are expired. Since the dose contained in these particles is negligible compared with those of larger radii, rebreathing of these particls is neither desirable nor useful. Apparatus presently available designed for rebreathing should be discarded for routine clinical procedures.

themselves and will never reach the trachea (See Figure 7). With particles ranging from 30 microns to 10 microns in radius, distribution occurs up to the terminal bronchioles as illustrated in Figure 2. Figures 3, 4 and 5 illustrate diagramatically what happens with particles of 3 to 10 microns in radius, particles from 0.5 microns to 3 microns in radius, and those below 0.5 microns in radius. Particles from 3 to 10 microns in radius reach the alveolar ducts, and are trapped there. Those below 3 microns in radius reach the alveolar sacs but not all of the particles are deposited to the same extent. About 50 per cent of those below 0.5 microns in radius are expired and are not therefore deposited in the lungs. Figure 6 illustrates what actually happens when iodized oil is atomized into the lungs (DeVilbiss No. 152). Note that all of the iodized oil is on one side of the chest. It is evident from our discussion of particle size distribution, that most of the iodized oil with an atomizer of this type must be baffled out by the trachea to form a liquid film on the surface of the trachea with only the very small particles which constitutes a comparatively minor fraction being breathed into the recesses of the lungs. Figure 6 discloses that these particles are insufficient to show up readily in the x-ray film. However, if they were antibiotic particles, it is conceivable some local therapeutic effect might be achieved by the convection of these very small particles into the lungs. To go back to the liquid film formed on the surface of the trachea by atomization of the iodized oil, this liquid is distributed through the lungs dependent upon gravitational forces. The mucosogram in Figure 6 shows all of the visualized iodized oil on one side, that is, the side to which the patient is tilted. Having shown that large particles will be distributed by baffling and gravitational forces within the lungs, we may now discuss the fate of atomized solutions with the DeVilbiss No. 251, with a known particle size distribution and of inhaled dust particles of different particle sizes.

Particle Size During Atomization

Table I, gives the drop-size distribution for the DeVilbiss No. 251 atomizer for 10 pounds of pressure per square inch using the method of measurement described in the foregoing. Although the number of particles below 5 microns in radius is large compared with the number of bigger particles, the number of these smaller particles as pointed out hitherto, does not give a sufficient indication as to the therapeutic potential. In order to obtain the dosage, he number of particles is multiplied by the cube of the radius of the particle. This then, gives a number which compares the volume or weight of the droplets. This value in the third column in Figure 1, is the comparative equivalent dose in a given volume of sprayed

TABLE I

DROP SIZE DISTRIBUTION DATA FOR DeVILBISS No. 251 ATOMIZER AT 10 lbs./sq. inch

Drop Radius, r. u	Number n	nr3	Per cent by Weight	Approximate Distribution in Lungs to:
0.65	1930	540	0.08	
1.30	1060	2300	0.39	Alveolar
2.60	750	13000	0.21	Sacs 0.68%
3.9	700	42000	0.69	
5.2	380	53000	0.86	
6.4	275	72000	1.16	Alveolar
7.7	164	75000	1.20	Ducts 5.91%
9.0	171	124000	2.00	
10.3	129	141000	2.28	
11.6	95	148000	2.40	
12.9	78	167000	2.84	
14.2	62	178000	2.78	
15.5	55	205000	3.30	
16.8	33	156000	2.42	
18.1	22	130000	2.10	
19.3	26	187000	3.03	Terminal
20.6	26	227000	3.56	Bronchioles
21.9	20	209000	3.26	
23.2	15	187000	3.02	
24.5	17	250000	4.04	
25.8	9	154000	2.50	
27.1	7	139000	2.25	
28.4	4	92000	1.50	
29.7	7	183000	2.98	
31.0	1	30000	0.47	
32.2	5	164000	2.66	
33.5	5	188000	3.03	
34.8	5	214000	3.04	
36.1	7	327000	5.29	
37.4	4	203000	3.28	
38.7	2	119000	1.82	
40.0	2	128000	2.07	
41.3	2	138000	2.23	
42.6	2	159000	2.57	Trachea
43.9	2	170000	2.75	
45.2	2	182000	2.84	
46.5	2	201000	3.25	
47.7	1	111000	1.70	
49.0	1	118000	1.80	
50.3	1	125000	2.02	
51.6	0	0	0	
52.9	1	149000	2.31	
54.2	1	157000	2.44	
58.0	1	195000	3.15	
		6138000		

To obtain number of drops formed from 1 cc. of solution multiply *Number* column by 38,400.

liquid. The per cent dose with an atomizer of this type is given in the fourth column for particles of different sizes. Note that with this type of drop-size distribution approximately 0.68 per cent of the dose may reach the alveolar sacs provided the spray is breathed in simultaneously with inspiration. This is an important point because if the initial phase of inspiration is not provided with a sprayed mist, much of the mist will be resident in the dead spaces of the lungs for a period with smaller particles breathed out. Assuming that spraying occurs with the initial phase of inspiration, we may now ascertain what happens to the rest of the particles. About 5.9 per cent of the particles may reach the alveolar ducts. The remainder is divided between the trachea and the terminal bronchioles. In other words, with an atomizer of this type, given suitable mechanical inspiratory conditions, more than 6 per cent of the material may be said to reach the recesses of the lungs if we define the recesses of the lungs as the alveolar ducts and the alveolar sacs.

Commercially Available Penicillin Powders

In Table II is given the particle size distribution of a penicillin powder commercially sold for inhalation therapy made by Manufacturer "X." In this case, the number of particles found in the smaller radii is also large but, when the per cent by weight is considered, less than 0.2 per cent of the sample of this powder sold

TABLE II

PARTICLE SIZE DISTRIBUTION OF PENICILLIN POWDER FOR INHALATION THERAPY (Manufacturer "X")

Particle Radius	Number of Particles	Per cent by Weight	Approximate Distribution in Lungs to:
0.25 - 1.2	734	0.00	
1.3 - 2.4	478	0.02	Alveolar Sacs 0.15%
2.4 - 4.0	330	0.13	
4.1 - 5.6	179	0.24	
5.7 - 7.2	111	0.36	
7.3 - 8.8	77	0.48	Alveolar Ducts 1.71%
8.9 - 10.4	58	0.63	
10.5 - 12.0	32	0.45	
12.1 - 13.6	24	0.51	
13.7 - 15.2	16	0.58	Terminal
15.3 - 16.8	13	0.66	Bronchioles 11.24%
16.9 - 32.8	53	9.04	
Over 32.8	29	86.63	Trachea 86.6%
TOTAL	2134		

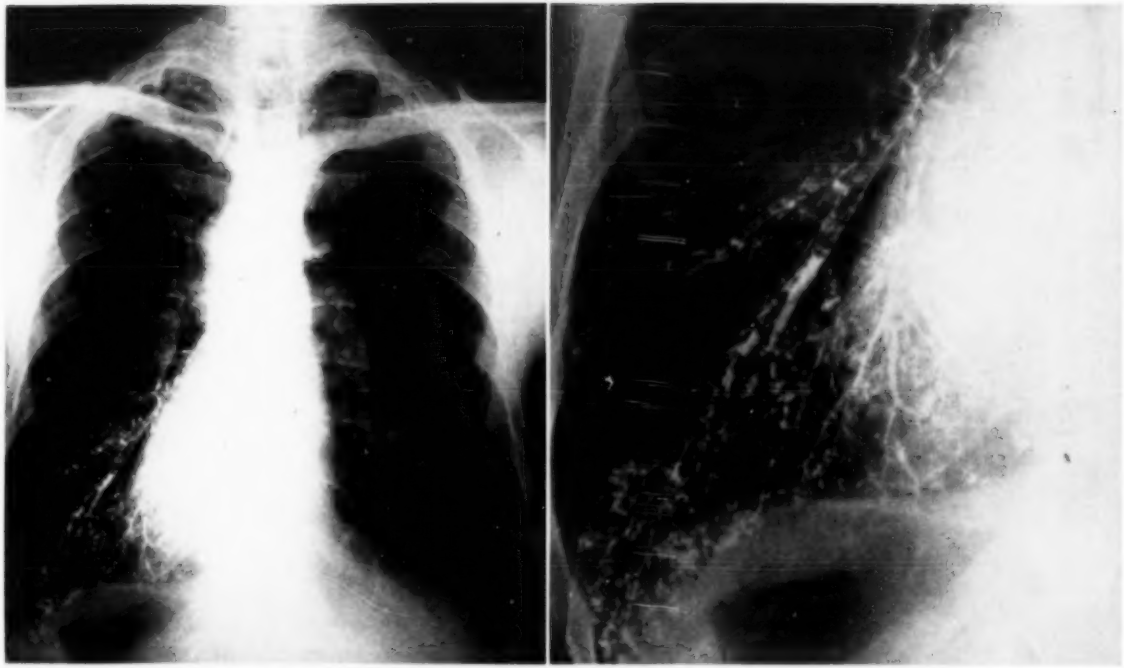

FIGURE 6a

FIGURE 6b

Figure 6a: Atomization bronchogram obtained with general technic of Fariñas (Unpublished data of Abramson and Schwartz).
Figure 6b: Atomization bronchogram of Figure 6a enlarged.

for inhalation therapy ostensibly to reach the recesses of the lungs, reaches the alveolar sacs with somewhat more than 1 per cent reaching the alveolar ducts. Indeed, the examination of the table reveals that less than 2 per cent of this powder or much less than the material atomized, or less than 2 per cent of the powder reaches the recesses of the lungs. Approximately 90 per cent of the powder would be retained by the trachea, if indeed the powder ever reaches the trachea. By far this larger fraction is probably deposited in the upper respiratory tract. The powder is sold to be taken either by the oral or nasal route. Certainly, most of this material is deposited in the nose if the nasal route is used and a great deal must be deposited in the pharynx. Now, it may be argued by the manufacturer that in view of the clinical results reported with this powder, some of the powder dissolves in the tracheal fluids and leaks down into the recesses of the lungs in the same way that the iodized oil does as depicted in Figure 6. This is a possibility which cannot be denied and which in all likelihood occurs to an unpredictable extent. But, it by no means makes the use of this powder, prepared in such a disadvantageous particle size distribution, desirable. It is much simpler not to depend upon an accidental distribution of the powder within the lungs depending upon the flow of the dissolved penicillin and tilting of the patient but rather on having the proper size distribution to begin with. Penicillin dusts of a lower mass median diameter are preferable.

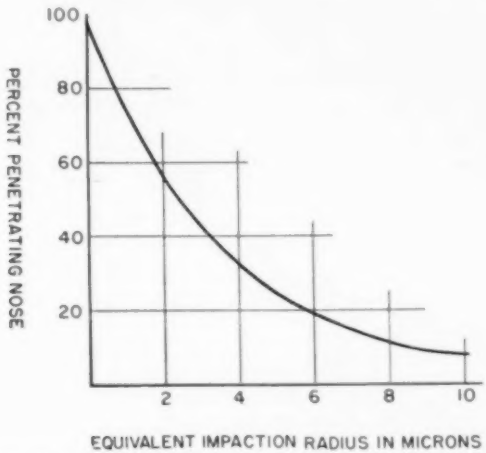

FIGURE 7: The data of Lindahl and Tracewell have been replotted. Note that with particles about 5 u in radius 80 per cent are deposited in the nose. With particles above 2 u in radius approximately 60 per cent are deposited in nose. Similar phenomena occur in the oro-larynx, thus reducing the dosage with large particles.

Table III, is an example of a commercially available penicillin powder more properly designed for inhalation therapy. This powder is ground to a much finer size. According to our method of calculation, 8 per cent of the powder is below 2.5 microns in radius and therefore will reach the alveolar sacs. Thirty-four per cent of the powder is from 2.6 to 7 microns in radius and therefore reaches the alveolar ducts. About 50 per cent of the powder is capable of reaching the treminal bronchioles with a small amount retained by the trachea. This particle size distribution provides a size spectrum of penicillin dust particles available to all parts of the res-

TABLE III

PARTICLE SIZE DISTRIBUTION OF PENICILLIN POWDER FOR INHALATION THERAPY (Manufacturer: Schenley)

Radius of Particles (u)	Per cent by Weight	Approximate Distribution in Lungs to:
0.5- 2.5	8	Alveolar Sacs 8%
2.6- 7.0	34	Alveolar Ducts 34%
7.1-15.0	42	
15.1-25.0	9	Terminal Bronchioles 51%
25.1-70.0	3	
70.1-99.0	3	Trachea 7%
More than 99	1	

TABLE IV

PARTICLE SIZE DISTRIBUTION OF PENICILLIN POWDER FOR INHALATION THERAPY* (Manufacturer: Lederle)

Diameter (u)	Per cent by Weight	Approximate Distribution in Lungs to:
Below 1.0	0.081	
1.1- 2.0	0.431	
2.1- 3.0	0.761	Alveolar Sacs 5.03%
3.1- 4.0	1.23	
4.1- 5.0	2.53	
5.1- 6.0	3.96	
6.1- 7.0	7.99	
7.1- 8.0	5.57	
8.1- 9.0	11.48	Alveolar Ducts 76.13%
9.1-10.0	1.62	
10.1-15.0	36.80	
15.1-20.0	8.79	
20.1-25.0	18.84	Terminal Bronchioles 18.84%

*From data kindly supplied by Dr. Taplin.

piratory tract. If maintained under suitable storage conditions, it should serve admirably to reach even the recesses of the lungs and act as a favorable procedure for inhalation therapy. Indeed, the entire respiratory tract is assured of coverage with penicillin powders. Table IV, a sample of another commercially available powder should have the same desirable properties and is also recommended for the same reasons.

The data in Figure 7 represent what impaction occurs in the normal nose. With the mucous membrane congested and with blockage of the nose, much more will be taken out than observable from the normal nasal route. For this reason every effort should be made to provide a particle size distribution small enough to reach the respiratory tract and to provide storage conditions which prevent aggregation of particles.

The data in this paper indicate that both atomization therapy by means of a properly constructed atomizer and by the inhalation of penicillin powders with suitable size distributions may serve as useful procedures for reaching the recesses of the lungs by means of antibiotic and other medicinal aerosols. In favor of atomization therapy is the greater predictability under storage conditions. In favor of therapy with dust is the fact that the particle size distribution may be readily conrolled by grinding and in addition the problem of synchronization with the initial phase of inspiration is automatically insured. Of course, the powder does not have the predictability under tropical storage conditions as either the nebulizer or the atomizer would have. At the same time, the powder, if storage problems were suitably solved, might have great military usefulness in treating gas casualties of the lungs. It is apparent that both methods of therapy are desirable and worthy of further exploration. But this exploration should be controlled by employing a suitable atomizer with known drop szie distribution, or antibiotic dusts with powders of measured and predictable particle size distribution. In this way therapeutic evaluation may be based not only upon a description of an improvement of the patient's condition but also, at least, a semi-quantitative notion of just where the dose of the antibiotic is deposited in the lungs themselves.

Discussion

In the foregoing paragraph, it was pointed out that the penetration of the nose by aerosols to reach the pharynx and recesses of the lungs is a complicated route. Recent experiments of Lindahl and Tracewell[7] have been employed to plot the curve given in Figure 7, which shows the per cent of various types of particles of corn oil, sodium bicarbonate, calcium phosphate, methylene blue and glycerol penetrating the nose as a function of the equiv-

alent impaction radius in microns. The data were obtained by drawing the particles at different volume velocities through the nose and collecting the effluent aerosols through the mouth. Observe in Figure 7 that at least 80 per cent of particles, 6 microns in radius and above, are taken out by the nose and when the particle radius reaches 10 microns, more than 90 per cent of the particles are baffled out. If the nasal route is used, it would appear that to obtain 50 per cent penetration in the nose, the particles must be approximately 3 microns or below. If we examine Table II, in the light of these data, the powder for inhalation therapy prepared by Manufacturer "X" has more than 90 per cent of the mass more than 10 microns in radius. At best therefore, less than 10 per cent of this material could penetrate the nose since in all likelihood at least 90 per cent of the material is deposited in the nose when the nasal route is used. Probably an equally significant fraction of the residue would be taken out by the oral cavity and larynx. These data change the picture to a much lesser extent for the data given in Table III. There, as well as in Table IV, it is evident that a considerable fraction of both powders can penetrate the nose or orolarynx and be deposited in various parts of the respiratory tract in accordance with the theory of Findeisen, illustrated in Figures 1 to 5. These data of Lindahl and Tracewell, then, provide additional evidence that powders of the type described in Table II, are unsuitable for therapy of the lower respiratory tract.

SUMMARY

1) The particle size distribution of the droplets of atomized liquids and three particulate dusts have been measured.

2) The particle size distribution of a commercially available atomizer, especially designed to produce small particles reveals that approximately 6 per cent by weight of the droplets produced by this nebulizer may reach the aveolar ducts.

3) Three samples of commercially available penicillin dusts designed for inhalation therapy show important differences in the particle size distribution. One of these dusts has particles so large that it is practically useless for therapy of the lungs. Two others have particle size distributions by which approximately 40 to 80 per cent of the particle weight may reach the aveolar ducts.

4) The difficulties of using dusts in connection with tropical storage and maintenance of suitable particle size distribution is pointed out. It is emphasized that if penicillin dust therapy is to be suitable at all, the particle size distribution to begin with must be so designed that penetration into the nose, oropharynx and larynx of a reasonable fraction should be possible.

RESUMEN

1) Se han medido, el tamaño de la destribución de las partículas de los gotitas del liquido pulverizado y de tres particulas de polvo.

2) El tamaño de las partículas destribuidas por el nebulizador común, del tipo especial que produce pequeñas partículas; se comprobó que approximadamente 6 por ciento, por peso de los gotitas producidos por el nebulizador, llegan hasta las conductos alveolares.

3) En tres muestras, de polvo de penicilina común, para inhalaciones se demostró diferencias en la distribución del tamaño de las partículas. Una de estas muestras tema particulas tan grandes, que prácticamente no tienen ningun valor terapéutico para los pulmones. Las otras dos, tienen una destribución del tamaño de las partículas, que se aproxima desde 40 a 80 por ciento del peso de las particulas puede llegar a los conductos alveolares.

4) Se recolca, la dificultad, cuando se usa polvos en depósitos tropicales y mantener una destribución del tamaño de las partículas. Se ha insistido también, que para el polvo de penicilina, sea adecuado la destribución del tamaño de las partículas, tiene que ser tal, que su penetración a travez de la nariz, boca, faringe y laringe, sea posible.

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Aspiration of Pleural Fluid*

MORRIS BRAVERMAN, M.D., F.C.C.P.†
Detroit, Michigan

A change in the routine manner of performing aspiration of pleural fluid is proposed. Justification for this change is made on anatomic, physiologic and pathologic grounds.

The lateral recumbent position for a chest tap, with the side to be aspirated dependent, has safety, speed and convenience to recommend it. Its greatest usefulness will be found in the treatment of the hydro-pneumothorax of pulmonary tuberculosis.

The spatial relationship of the anatomic structures to the eye of the aspirating needle, with the patient in the sitting or vertical position, is often such as to leave little working space for a safe maneuver (Fig. 1).

This is particularly true when an operator desires to aspirate a maximum amount of pleural fluid from a patient in the sitting position, and, who has either a simple hydrothorax or a hydropneumothorax. It is then that so many insert the needle into the most dependent portion of the pleural space. If the floor of the narrow pleural space rests immediately upon the diaphragm, or is formed by the lung and its visceral pleura and the chest wall, the dangers of a chest tap with the patient erect are obvious (Figs. 2 and 3). Accidental pulmonary or hepatic punctures have occurred. In such a position traumatic manipulation of the diaphragm and its pleura during the end of a chest tap may cause shoulder pain.

It often becomes necessary to aspirate pleural fluid from a febrile and weakened patient. The procedure may have to be temporarily halted or stopped altogether, if the patient has been sitting and feels faint, has fainted or is too weak. By the use of the lateral recumbent position such a time consuming and annoying embarrassment can be avoided. During the dozen years that the writer has used the lateral recumbent position, he has not had a single instance of fainting.

By placing the patient in the lateral recumbent position we immediately accomplish a favorable and safe anatomic spatial relationship to the eye of the aspirating needle (Figs. 4 and 6). We elect the wide expanse of the lateral chest wall to serve as a

*From the William H. Maybury Sanatorium (Detroit Municipal Sanatorium), Northville, Michigan.

†Formerly resident physician and later attending physician at Wm. H. Maybury Sanatorium.

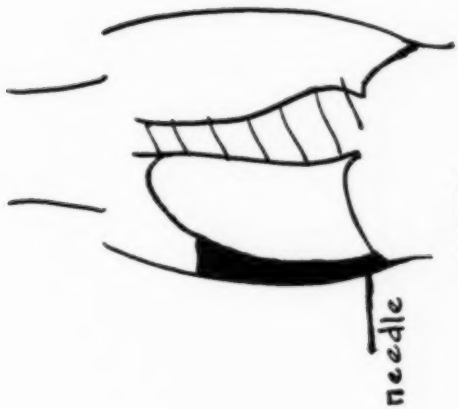

FIGURE 2

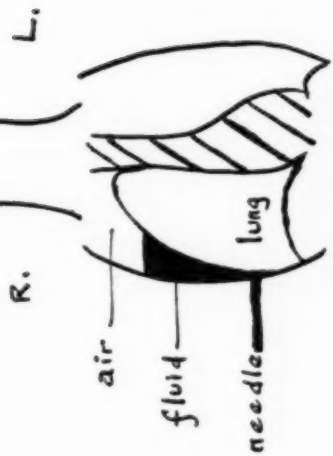

FIGURE 1

floor to the aspirating space and choose with greater safety an entrance point.

Figures 4, 6 and 7 indicate the ease with which pleural fluid may be made to flow or assume a position of greater safety for its removal. It is more advantageous to insert the needle near the upper axilla with the patient so placed that the flow of fluid from any pleural pocket is towards the shoulder trough of the free pleural space. As frequently occurs the hydropneumothorax is distributed in multiple pockets. Then it becomes an arduous and oft repeated task to safely drain each pleural pocket (Fig. 5) in the sitting position.

The lateral recumbent position for aspiration may be accomplished in a number of different ways. A very ill patient may be left in bed or on a stretcher and helped to the edge. The operating room table may be used in a like manner. Some operating room tables can be altered so that a sliding section near the middle edge may be removed so the lateral chest wall is freely exposed. Others prefer to use unaltered existing equipment. A stationary smaller table placed obliquely to a larger tilting type operating table may serve admirably. The patient's head and shoulder rests on the smaller table while the rest of the body in a lateral recumbent position is on the larger table. The lateral chest wall then lies across the open V-shaped area between the two tables. The operator will find it convenient to be seated close by on a chair.

One objection an operator may have to the lateral recumbent

FIGURE 3

FIGURE 5

FIGURE 4

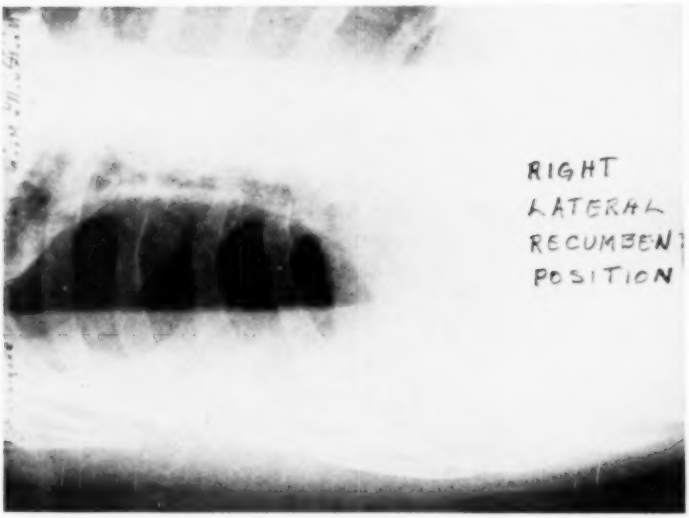

FIGURE 6

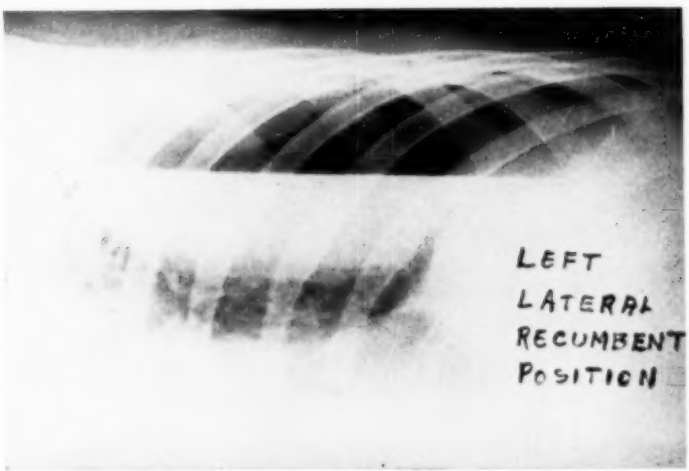

FIGURE 7

position is his own initial difficulty in orientating himself to the new method of approach. This objection can be met by the satisfaction of doing an aspiration safely, quickly and with less effort. Single residual clavicular level of pleural pockets of fluid most often have to be aspirated with the patient in a sitting position.

Acknowledgement: The author is grateful to Dr. Leonard Howard, Superintendent, William H. Maybury Sanatorium, Northville, Michigan, for his helpful suggestions in the preparation of the manuscript.

SUMMARY

1) A change in the routine manner of positioning the patient from the vertical or sitting to the lateral recumbent method of approach is proposed.

2) The lateral recumbent position for doing a chest tap, with the fluid side dependent, has safety, completeness, speed and convenience.

3) By placing the patient in the lateral recumbent position, we elect the wide expanse of the lateral chest wall to serve as a floor to the pleural space, and, choose with greater safety an entrance point for the eye of the aspirating needle.

4) The lateral recumbent position is most useful in the treatment of the hydropneumothorax of pulmonary tuberculosis.

5) Febrile and weakened patients particularly, who need a chest tap, tolerate the lateral recumbent position well.

RESUMEN

1) Se propone un cambio en el modo de colocar habitualmente al enfermo, que en lugar de ser puesto en posición sentado para la punción pleural se ha de colocar en decúbito lateral.

2) La posición en decúbito lateral para la punción torácica permite que el líquido se alcance en su punto declive. Es segurá, rápida, conveniente y más completa la extracción.

3) Colocando el tórax así, hacemos que la parte más voluminosa del tórax sirva de piso a la colección por extraerse y la aguja entra con más seguridad.

4) La posición descrita es la más útil para tratar el hidroneumotórax.

5) Especialmente los enfermos debilitados o febriles toleran muy bien esta posición para la punción.

Non-Bacterial Pneumonias*

JEROME T. SYVERTON, M.D.†
Minneapolis, Minnesota

Respiratory infections, inclusive of pneumonia, have long constituted a medical problem of the first order. These afflictions continue to exceed all other diseases in the loss of time from industry and from schools.[32] Despite the means for the therapeutic conquest of pneumococcal infections and of most of the other bacterial pneumonias,[44] the complex of pulmonary infections designated clinically and pathologically as pneumonia has remained fairly constant in incidence, and has maintained its role as a major cause of death.[29]

The importance of the non-bacterial pneumonias as a component of the group is of recent recognition.[1-19,22-28,30-39,43] It has been estimated that from 5 to 70 per cent of all pneumonias are non-bacterial. The percental number, of course, depends on the source of patient, i.e., whether from general practice, military service, industrial practice, or hospital practice.

Much of the information concerning non-bacterial pneumonias is recent. It is especially because of the studies reported within the past decade that the causative agents of non-bacterial pneumonia are known to include a wide variety of microbiologic agents and their products, such as viruses, rickettsia, fungi, protozoa, toxins and allergens. A relationship to the pneumonic process of many of these agents is newly recognized. Many factors are responsible for the disentanglement and recognition of successive etiologic entities from the complex. The stimulus for concerted and cooperative effort which was provided by World War II is outstanding. Moreover, the process has been facilitated 1) by the ready availability and common employment of chemotherapeutic and antibiotic agents for treatment, thereby eliminating effectively most bacterial agents; 2) by the increasingly frequent use of roentgenography for the study of any case of suspected pneumonia; 3) by a realization in hospital practice that the need is for more, rather than less, precise bacteriologic diagnosis, because of the specificity of antibacterial agents and the possibility through adaptation of the appearance of resistant bacteria; and 4) by the

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†Professor and Head, Department of Bacteriology and Immunology, University of Minnesota.

development and application of new diagnostic laboratory methods.

It is the purpose of this paper to emphasize the characteristics which make it desirable to consider this wide variety of etiologic entities collectively as non-bacterial "virus-type" or interstitial pneumonias and, secondly, to point out the diagnostic laboratory tests that are available for their separation. The accepted bacteriologic diagnostic measures are inadequate in the study of non-bacterial pneumonias to establish a specific diagnosis, but are essential for the elimination of known bacterial agents.

The range of causative agents, the etiologic entities, and the epidemiologic characteristics of the disease complex are shown in Table I.

It may be seen from this table that many causative agents and etiologic entities are assembled in the category of "non-bacterial pneumonia." However different these infections appear to be, they should be considered collectively, because of essential similarities in their roentgenographic and pathologic pictures. Moreover, the clinical differentiation of any of the entities within the group from each other and from certain bacterial pneumonias is usually difficult or impossible.

Characteristics in Common

Pathology:

A review of the pathologic alterations which occur in the different types of non-bacterial pneumonias will make readily understandable the basic similarities in the pathologic, roentgenographic and clinical pictures. Such differences in the pathologic picture, as are observed for different entities, are no greater than may be found among cases of the same entity. Grossly, an infected lung may show little change, except for an increase in weight. The pleural surface may be smooth or show patches of fibrinous exudate. On section, the pneumonic areas vary markedly in size, distribution, and stage of evolution. Areas of atelectasis and emphysema are commonly apparent.

Histologically, the picture is that of an acute interstitial monocytic pneumonitis. The process probably starts as a bronchiolitis to extend locally from the regional interstitial tissues to involve the peribronchiolar tissues, the alveolar walls, and the pulmonary septa. The succession of changes which occur within the process extends peripherally from any given focus and results in the oldest and most advanced lesions being found immediately adjacent to the sites of origin, i.e., the small bronchioles. This succession of changes is about as follows: The alveoli immediately adjacent to the bronchiole fills with edema fluid and occasional polymorphonuclear leucocytes. The edema fluid in such alveoli is replaced

TABLE I

Non-Bacterial Pneumonias

Etiologic Agent	Pandemic	Epidemic	Endemic	Sporadic
Virus	Influenza (?)	Influenza A Influenza B	Lymphocytic Choriomeningitis Smallpox Varicella Psittacosis* Ornithosis* Meningopneumonitis* Human SF Pneumonitis* Illinois Pneumonitis*	Inclusion-body Pneumonia Lymphogranuloma Venereum*
Rickettsia			Q Fever	
Fungus			Histoplasmosis Coccidioidomycosis	
Protozoa				Toxoplasmosis
Allergen			Bagassosis	Rheumatic Fever
Unknown probably virus		Atypical Pneumonia Acute Pneumonitis Grippe Acute Catarrhal Fever "Flu" Viroid	Inclusion Body Pneumonia of Infants (Adams) Infectious mononucleosis	Erythema multiforme

*Basophilic group.

by mononuclear leucocytes until the alveoli are distended with mononuclear cells. The mononuclear cells appear to result from desquamation of the mucosal lining and from proliferation. The result is an interstitial pneumonitis. Ulceration of the mucosal lining of the bronchioles and of alveoli may be quite extensive. For certain types of non-bacterial pneumonia, the application of Mallory's technic for demonstrating connective tissue reveals that proliferative changes are limited to cells lining the alveoli. There is no apparent involvement of the connective tissue elements. The larger bronchi may not escape the inflammatory process. Evidence of involvement of the bronchial mucosa is shown by intense erythema, cellular infiltration by mononuclear leucocytes and a few neutrophiles in the absence of bacteria. Resolution of the pneumonic process within the parenchyma of the lung takes place from the more peripheral portion of the lesion toward the center. During resolution, the alveolar lumina commonly fill with an exudate which is made up of degenerate epithelial cells, mononuclear cells, and a few polymorphonuclear leucocytes. It is at that stage that bacteria of various kinds may be observed. Emphysema and atelectasis occur as sequelae. Desquamation of epithelium from mucosal surfaces to result in ulceration undoubtedly contributes to the bronchiectatic result.

Roentgenological Aspects:

Roentgenologic inspection[17,33,36] of the chest frequently reveals the first evidence of pulmonary involvement. Lesions are almost regularly demonstrable within the first few days of illness.

A distinctive feature of this pneumonic involvement is the variability in the type and size of the lesion. Characteristically, the inflammatory reaction is not sharply defined, as shown by an opacity which tends to merge imperceptibly with the surrounding pulmonary tissues. This density, which is variable, may remain stationary until resolution occurs, or may act as a focus of spread from which the lesion extends peripherally. Transitory changes are common, as illustrated by mottled densities which appear to disappear within 24 hours. Lesions may be confined in a single lobe or may occur in multiple lobes.

The pneumonic process commonly shows a predilection for the hilar region, either unilaterally or bilaterally, with radial extension outward into the peripheral portion of the lungs. These fan-shaped opacities are accompanied by increased bronchovascular markings. Varying degrees of acute tracheobronchitis are commonly present, as reflected by bilateral increase in the hilar and trunk shadows with indistinct outlines, soft mottling about the hilum, and generally hazy lung fields.[17]

TABLE II
Symptomatology in 1833 Cases of Non-Bacterial Pneumonia

Authority[33]	1941 Lyght[22]	1942 Green[15]	1943 Campbell[3]	1943 Young[43]	1944 van Ravenswaay[30]	1944 Commission[4]	1945 Curnen[6]	1946 Painton[26]	1946 McCoy[23]
Number of Cases	300	80	200	40	297	69	106	321	420
	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
Onset Gradual			63	most	67	26	73	70	
Cough	80	88	51	100	86	99	98	66	95
Malaise	60	42	25	80	70	77	61	33	34
Headache	55	47		80	48	78	65	20	25
Chills	50	48		50	68	75	59	30	42
Coryza	30			20	49	41		60	3
Sore Throat	30	20	26	70	47	36	30	25	25
Sputum					74	81	82	20	
Bloody Sputum	4	14	6		26	10	25	3	
Dyspnea	5	9	3	30	21		5		0.5

Apart from the hilar fan-shaped shadow, which is the more commonly observed lesion, other variations consist of less well defined lesions which may occur in any portion of the lung field. These include such changes as multiple small areas of soft diffuse infiltration that increase in size over a period of days to become irregularly confluent; a diffuse, somewhat coarse mottling, indistinguishable from tuberculosis, especially when it involves the apical regions; and circumscribed foci more commonly in the periphery of the lung field, which are not so dense as the consolidation of lobar pneumonia or the opacity of a neoplastic process.

Atelectasis occurs as a natural alteration in the pathogenesis of pneumonic process and as a complication. As an example, Campbell, et al,[3] in a study of 200 unselected cases of atypical pneumonia which occurred during an epidemic of this disease at Fort Eustis, Virginia, reported that the impression of atelectasis was substantiated roentgenographically for 19 per cent of these cases by a shift of the mediastinal structures or by an elevation of the diaphragm towards the site of the lung involvement. Exceptionally, an entire lobe becomes atelectatic to suggest lobar pneumonia, but other findings reveal the true atelectatic nature.

Clinical Aspects:

The pathogenesis of the pneumonic process makes one suspect wide variation in the clinical manifestations of the non-bacterial pneumonias. Such, indeed, is the case. The symptomatology in 1833 cases of non-bacterial pneumonia, as compiled from reports in the literature,[33] are summarized in Table II.

It can be seen from this chart that the onset of illness in approximately two-thirds of patients was gradual and ill defined. Initially, the onset frequently was indistinguishable from that of a cold or grippe. Cough, malaise, headache, and chills were common early complaints which persisted throughout the acute illness. Coryza and sore throat were present less commonly. The cough was frequently accompanied by substernal discomfort or pain and more usually became productive of mucopurulent sputum, which at times was blood tinged. In some series of cases, bloody sputum had been present in as many as a fourth of the cases.[6,30]

The physical findings for these same 1833 cases[33] are summarized in Table III.

The ill defined character and obvious overlapping that most of the symptoms and signs which have been selected as outstanding illustrate the hazards of clinical classification and emphasize the impossibility of separating positively on the basis of symptomatology or clinical signs the non-bacterial pneumonias from pyo-

TABLE III

Physical Findings in 1833 Cases of Non-Bacterial Pneumonia

Authority[33]	1941 Lyght[22]	1942 Green[15]	1943 Campbell[3]	1943 Young[43]	1944 van Ravenswaay[30]	1944 Commission[4]	1945 Curnen[6]	1946 Painton[26]	1946 McCoy[23]
Number of Cases	300	80	200	40	297	69	106	321	420
	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
Fever		73		55	97	81	95	90	63
Pharyngitis		65				61	69	60	
Rales		92			56	93	93	60	81
Dullness		58			28	41	54	20	28
Lymphadenitis		5		several			24		

genic bacterial pneumonias, tuberculosis, tularemia, brucellosis and neoplastic infiltration of the lung, among others.

The variation in clinical manifestations in individual patients with the same disease and among patients suffering from different entities included in the category of non-bacterial pneumonia is understandable, since the disease primarily involves the mucous membrane of the respiratory tract with symptoms and signs in

TABLE IV

Spectrum of "Respiratory" Infections

Immune carriers
Inapparent infections
Sporadic attacks
Mild URI without systemic involvement
Mild ambulatory forms
Ambulatory forms with pneumonitis
Severe systemic involvement without pneumonia
Systemic involvement with pneumonia

TABLE V

Non-Bacterial Pneumonias

Vehicle:	Minute invisible droplets
Mode of Entry:	Inhalation via nose and mouth
Site of Primary Attack:	Mucous membrane of the respiratory tract
Dominant Localization:	Rhinitis
	Pharyngitis
	Tonsillitis
	Laryngitis
	Tracheitis
	Bronchitis
	Bronchiolitis
	Pneumonitis
	Systemic involvement with or without RI
	Gastrointestinal involvement with or without RI (respiratory infection)

TABLE VI

Misdiagnoses of Non-Bacterial Pneumonias

Mild Bacterial Pneumonia	Threatened Pneumonia
Atelectasis	Touch of Pneumonia
Broncho Pneumonia	Congestion of Lungs
Bronchitis	Spot on the Lung
Bronchiolitis	Unrecognized

any given case reflecting the predominant site of localization of that involvement. The spectrum of "respiratory" infections that may result is listed in Table IV.

A better understanding of the variation in reaction among hosts can be reached by pointing out, as shown in Table V, that the vehicle for infection consists of minute invisible droplets which are inhaled by way of the nose and mouth to reach the mucous membranes of the respiratory tract. The results of infection are reflected by an inflammatory reaction which subsequently may be categorized as rhinitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonitis, or any combination thereof. Moreover, there may result systemic involvement, with or without respiratory symptoms, or intestinal involvement, with or without respiratory symptoms.

It is apparent from Table V that classification on the basis of dominant anatomic involvement is no more than suggestive insofar as the causative agent is concerned.

It is to be emphasized that a wide spectrum in the clinical, pathologic, and roentgenographic manifestations of an acute respiratory infection may result from a single etiologic agent and that any epidemiologic study involving a causative agent of non-bacterial pneumonia must recognize the complexity of this spectrum. It is only by means of a precise laboratory diagnosis that separation of the many entities which are represented can be brought about. These entities in the past, for the most part, have been conveniently side-tracked by attaching any of a variety of misdiagnoses, of which a few are listed in Table VI.

Differential Diagnosis of Non-Bacterial Pneumonias

The essential similarity in the usual roentgenographic and pathologic pictures of the members of the group of respiratory infections which are manifest as non-bacterial pneumonias has been emphasized. Epidemiologic, clinical, roentgenographic, and pathologic studies may serve for allocation within the group, but differentiation from one another and from certain bacterial pneumonias is usually difficult or impossible. An isolated sporadic case especially demands precise diagnostic measures. It is important, therefore, to learn what criteria can be employed for disentanglement of the group. It can be seen from Table I that the members of this group fall into at least five categories: pandemic influenza, epidemic influenza of types A or B, the psittacosis-lymphogranuloma venereum sub-group, the atypical pneumonia sub-group, and a sub-group which is made up of the remaining entities. Each of these entities will be considered summarily, so as to emphasize the salient characteristics of each.

Influenza:

What is meant by the term "influenza"? Any physician when asked this question knows what he means by influenza, but, when pressed for a definitive answer, commonly that answer is inexact and all-inclusive. It is apparent that the term "influenza" is used in clinical medicine with three distinct and frequently confused meanings: First, there is the use of the term in a wide and general sense in which it serves merely as a convenient label for any upper respiratory infection showing systemic involvement, a leucopenia, and being of an unknown or unrecognized etiology. This latter application of the term "influenza" is more commonly applied by older physicians who reflect their experience in the 1918 epidemic by using the term "flu" more commonly than younger physicians who accept and write off the same type of illness as "atypical pneumonia," "viral pneumonia," or "cat fever." The second use of the term "influenza" is in a restricted and specific sense to designate cases which are established as being of known virus etiology by the recovery of the virus of influenza A or the virus of influenza B, or by the demonstration of specific influenzal antibodies. It is common epidemiologic practice today to designate as epidemic influenza any unusual increase in the number of respiratory cases which satisfy the general criteria of clinical influenza, occur abruptly in numbers, show high communicability, and yield a specific virus type from one or more cases. It is well established that the viruses of influenza, type A and type B, cause disease clinically indistinguishable from each other and from the causative agents of other non-bacterial pneumonias. Specific identification of A or B virus is established by the isolation of the virus or by the demonstration by neutralization test, by complement-fixation test, or by the practical and more commonly applied Hirst hemagglutination test of an increase in antibody titer during convalesence. The third use of the term "influenza" is in reference to pandemic influenza. The single criterion which is available at present for distinguishing pandemic influenza from a host of "imitators" is its capacity for rapidity of spread, i.e., to take a continent or two at each stride. Pandemic influenza is a tremendously important virus disease. Of the three great pestilences of mankind, smallpox, plague and influenza, influenza alone continues to be a constant and immediate threat to man in all parts of the civilized world.—Why? The answer is in the unlimited potentialities of this disease. As an example, let us consider the most recent pandemic, 1918-1919. The final statistics of that pandemic as released by the League of Nations shows that at that time one out of four persons, 500 million out of a population of 2 billion,

had the disease and that of these about 15 million died. The mortality rate at the height of the pandemic was one out of 50 persons in the world per month, which is a death rate unsurpassed in history. Influenza killed more in a few months than the first World War in five years or during the entire second World War. In the United States, there were 20 million cases with 450 thousand deaths in six months. Pandemics similar to that of the 1918 pandemic have recurred over the past 425 years at intervals of from 25 to 60 years.

Pandemic influenza is rightfully considered to be a respiratory disease, and yet, in the early stages of the pandemic, there frequently were no symptoms referable to the respiratory tract. Pandemic influenza is characterized by a short incubation period of from 24 to 48 hours, an abrupt onset, headache, chilly sensations, loss of appetite, sometimes nausea and vomiting, fever of from 101 to 105 degrees F. and commonly limited to three days duration. Muscular pains and leucopenia are characteristically present. Bacterial superinfection, which is common, was assumed to have been responsible for the high mortality rate in the 1918 pandemic. The bacteria implicated were *Streptococcus hemolyticus, Staphylococcus aureus,* and *Hemophilus influenzae*. Convalescense is slow and protracted with marked weakness and mental depression being characteristic features.

The cause of pandemic influenza was unknown in 1918 and is unknown today. The 1918 pandemic stimulated many careful bacteriologic investigations. The results of these studies can be summarized by stating that their yield was limited to a better statistical basis for accepting or rejecting subsequent work. It has been assumed following the pandemic of 1892 that *Hemophilus influenzae* was the causative agent. This microorganism and other bacterial agents were effectively ruled out, except as secondary invaders. The recovery by Shope in 1931 (see reference 38 for a review of the literature) of influenza virus, type A, from an infection of swine closely resembling human influenza led to the isolation by Smith, Andrewes and Laidlaw of a similar virus from cases of human influenza in 1933 and by Francis in 1940 of influenza virus, type B. It was assumed by some that the causative agent of pandemic influenza had been isolated. Influenza virus, types A and B, have been shown in subsequent years to be world-wide in distribution and to be responsible for epidemics at fairly well established intervals. It should be recognized, however, that the relationship to pandemic influenza of existent viruses, even though the latter are called "influenza viruses," is conjectural. On the assumption that among these viruses one may be related to pandemic influenza and to bring about a better understanding of

epidemic influenza, measures for the immediate identification and control of influenza in pandemic form are in existence in this country.[45] A national network of regional laboratories is prepared to isolate and to identify strains of virus from current outbreaks of influenza for supply to other laboratories which are equipped for large-scale vaccine production and for other studies.

Primary Atypical Pneumonia:

The clinical syndrome commonly diagnosed as primary atypical pneumonia is a noncommittal designation for acute disease of the respiratory tract which may be manifest as an acute tracheobronchitis or as an interstitial pneumonia. The disease is variable in clinical manifestations and in the severity of the symptoms it provokes, and, therefore, atypical pneumonia as observed in isolated cases is indistinguishable from the other entities that belong in the group of non-bacterial pneumonias.

The many carefully controlled studies which have been carried out with this disease in the past decade have been the subject of numerous reports and reviews. Many reports, such as the outstanding work of Dingle and other members of the Commission on Acute Respiratory Diseases,[4,9] of Horsfall,[16] and of others make it apparent that primary atypical pneumonia is of common occurrence.

The Commission on Acute Respiratory Diseases reported successful transfer of primary atypical pneumonia to human volunteers by employing bacterial filtrates of sputum and throat washings as source material. It was not established by these workers, however, whether one agent or multiple agents may be concerned in the production of the disease under natural conditions.

Even though evidence for the virus causation of primary atypical pneumonia has been demonstrated, the diagnosis at present rests on the exclusion of other similar diseases. Two serologic tests provide ancillary supportive evidence when positive. These tests are the cold hemagglutinin test[9,22,35] and an agglutination test for *Streptococcus MG* antibodies.[34,35] The success of each of these tests depends on the demonstration of a rise in the respective titer of either antibody when samples of serum representative of the acute and convalescent phase of the patient's illness are assessed for the presence of agglutinins. The demonstration of cold hemagglutinins utilizes Group O red blood cells as antigen. Agglutination of these erythrocytes takes place at ice-box temperature but not at 37 degrees C. The second test is carried out in essentially the same fashion as other bacterial agglutination tests by employing as antigen *Streptococcus MG*, which is a serologic type of indifferent streptococcus related antigenically to

Streptococcus salivarius. Significant increases in the titer of either antibody, rarely both, occur in about 50 per cent of the cases of primary atypical pneumonia. The presence of agglutinins for these two unrelated antigens occurs independently. It has been suggested that each may possess antigenic components in common with the etiologic agent of primary atypical pneumonia.[8]

The Pneumonitis-Psittacosis-LGI Sub-Group:

The members of this sub-group are commonly classified as viruses, but they possess common biologic properties which separate them from other viruses and set them apart as intermediate between rickettsiae and viruses.[24,25] Thus, in contrast to other viruses, they are much larger, stain readily with simple basophilic dyes, undergo successive developmental stages to form large basophilic cytoplasmic inclusion bodies in endothelial and epithelial cells, and are sensitive to sulfonamides and antibiotics. The host range includes a wide range of mammals and birds to result in infection characterized by an immunity-infection status.

The best known agents in this group are: a) the pneumonitis viruses, such as meningopneumonitis, Baker's feline pneumonitis, pneumonia virus of mice (PVM), mouse pneumonitis (SF), Louisiana pneumonitis; b) psittacosis and ornithosis; and c) lymphogranuloma inguinale. Infections in man, excepting lymphogranuloma venereum, are characterized by involvement of the respiratory tract. Pneumonia also occurs in lymphogranuloma venereum.

Diagnosis within this sub-group is established by the isolation and the identification of the causative agents. Mice, cotton rats, hamsters, guinea pigs, pigeons and other birds, and embryonated eggs are readily susceptible to infection. Mice are commonly employed for cross-immunity and cross-neutralization tests. The complement-fixation test is employed as a diagnostic aid, but it is limited in its application because of the possession by members within the group of antigenic components in common. This test, thereby, becomes unreliable as a specific diagnostic aid unless a sharp change in titer during early convalescence supports the clinical findings. Contributory evidence to support a diagnosis in this group sometimes is found in the epidemiologic studies which demonstrate factors of contact with natural hosts.

Q. Fever:

Q fever is a rickettsial infection which was first recognized as a human disease in 1935 in Australia.[7] The causative agent was recovered from naturally infected ticks, *Dermacentor andersoni*,[8] at about the same time in the western United States. The disease has since been found to occur in the Mediterranean area, in North

America, and in Central America. Recent reports[37,18] show that Q fever is endemic in California, where from 10 to 20 per cent of the dairy cows in the Los Angeles area were found to possess serum antibodies for Q fever and more than a hundred human cases were diagnosed. The clinical and roentgenographic pictures are essentially similar for what has been outlined for the non-bacterial pneumonias with certain exceptions, i.e., the onset may be more sudden, symptomatic recovery more rapid, and symptoms referable to the upper respiratory or gastrointestinal tracts are not conspicuous.

Acute Lymphocytic Choriomeningitis:

An incubation period of from seven to 21 days is followed by the primary phase of the disease of from seven to 20 days duration of an influenza-like syndrome with viremia, sore throat, tonsillitis, cough, bronchitis, and pneumonic changes consistent with what has been described for the other non-bacterial pneumonias. This phase may or may not be followed by involvement of the central nervous system.[10,19]

Miscellaneous Group of Pneumonias of Viral Origin:

Measles: Interstitial pneumonia has long been recognized as an integral part in the pathogenesis of measles. Shadows, suggesting infiltration of the lung, are present in from about 10 to 50 per cent of the cases. As in the other non-bacterial pneumonias, the physical signs may be absent in about half of the cases.

Variola and Vaccinia: Pneumonia may occur in smallpox and generalized vaccinia. Lillie[20] and Lillie and Armstrong[21] have reported that pneumonia in variola and vaccinia results primarily from the virus itself, and, like the dermal lesions, pyogenic bacteria invade secondarily to give rise to the suppurative changes which are commonly accepted as complications.

Other Viral Pneumonias: Varicella pneumonia and certain pulmonary infections in infants are accepted as being caused by viruses, although the causative agents have not been demonstrated.[2,14] Evidence of virus causation consists of the presence of intranuclear inclusion bodies in the epithelial cells of the respiratory tract.

Adams and his co-workers[2] have studied over a period of about 10 years a pneumonitis of infants which presumably results from a primary virus infection. This pneumonitis is interstitial in type and is characterized by the presence of cytoplasmic inclusion bodies in epithelial cells. It may occur as a sporadic case and in localized epidemics.

Fungous Pneumonias:

Histoplasmosis: Among the protean clinical manifestations of histoplasmosis is a pulmonary type with cough, sputum, night sweats and chest pain, which may stimulate other forms of non-bacterial pneumonia.

Coccidioidomycosis: Tracheobronchitis and pneumonitis of the interstitial type occur as one of the manifestations of the primary infection with *Coccidioides immitis*. The concomitant symptoms of headache, general aches and pains, sore throat, and slight fever lead to a diagnosis of non-bacterial pneumonia.

Toxoplasmic Pneumonia:

The protozoan parasite, *Toxoplasma hominis*,[28] gives rise to an infection in adults which may have many features in common with atypical pneumonia, Q fever, and other non-bacterial pneumonias.

Allergic Pneumonias:

The causative factors which are responsible for the pneumonias seen in rheumatic fever, bagassosis, tropical eosinophilia, and Loeffler's syndrome are not understood. It is assumed by many that allergens are responsible.

TABLE VII

The Laboratory Diagnosis of Virus Diseases

Criteria to be fulfilled before a virus is acceptable as the causative agent of a given disease:

I. The virus must be regularly recoverable from cases of the disease and its distribution in the host's tissues must be in accordance with the lesions observed.

II. The virus must reproduce the disease in susceptible hosts.

III. Evidence for multiplication of the virus must be demonstrated by its transfer to susceptible hosts (or cells) in series with successful reproduction of histopathologic changes.

IV. Specific identification of the virus is accomplished by careful study of its:
   1) histopathologic changes
   2) host range
   3) pathogenicity by different routes of infection
   4) tissue affinities (cellular tropism)
   5) antibodies, as measured by one or more of the following techniques:
      a) protection tests (neutralization tests)
      b) complement-fixation tests
      c) precipitin or flocculation tests
      d) chicken red-cell inhibition test (Hirst test)
      e) heterophile, etc., tests for related antibodies.

Laboratory Diagnosis

The diagnosis of an isolated sporadic, mild, or severe, respiratory infection which may manifest itself as a non-bacterial pneumonia is difficult,[39] if not impossible, especially when the criteria for diagnosis are delimited by epidemiologic, clinical, and roentgenographic studies. It becomes apparent, therefore, that further progress in the diagnosis and treatment of the non-bacterial pneumonias must be brought about by developing and by utilizing efficient methods for etiologic diagnoses.

The objectives and the criteria to be fulfilled before a virus is

TABLE VIII

Laboratory Tests Employed Routinely in the Diagnosis and Treatment of Bacterial Pneumonias

(I) *Bacteriological Studies:*

A. Sputum
1. Record description of:
   a. gross appearance
   b. microscopic appearance of fresh smear preparation
2. Stain smear preparations by Gram and Acid-fast technics
3. If diplococci are abundant, do direct "quellung"
4. Culture on rabbit blood agar plate
5. Inoculate mouse by intraperitoneal route with 0.5 ml. sputum

B. Nose and Throat
For culture on rabbit's blood agar plate, transfer flora from oropharynx and from nasopharynx, utilizing a small cotton swab for each.

C. Blood
Withdraw 40 ml. for bacteriological and chemical studies. Culture a 10 ml. sample of blood, utilizing the pour plate technic for 5 ml. and 5 ml. for transfer to 100 ml. of beef infusion broth.

(II) *Hematological Studies*

A. Hgb, RBC, WBC, Differential

B. Chemistry	Serum	Citrated Blood
1. Plasma spec. grav.	3 ml.	
2. T. P. A/G	5 ml.	
3. Chlorides	10 ml.	
4. Carbon dioxide	under	
5. Icteric Index	oil	
6. NPN		3 ml.
7. SAD (if history of SAD therapy)		5 ml.

(III) *Other Studies*

A. Urinalysis
1. Routine
2. Culture of WBC and bacteria are present

B. Radiograph PA Chest

acceptable as the causative agent of a given disease are outlined in Table VII.

To better illustrate the laboratory diagnosis of a complex that falls into the category of "non-bacterial pneumonia," a case history and the subsequent laboratory studies will be outlined.

Case 1: M.B., a 25 year-old colored laborer was brought into the Emergency Division acutely ill. He first noticed aching throughout his body, fatigue and some dryness of his throat 24 hours before admission. About 12 hours later, he felt feverish, had repeated mild chills, and experienced greater general muscular aching. A moderately severe chill 2 hours before admission was followed by anorexia, severe frontal headache, a dry nonproductive cough and pain in his right chest. Physical examination revealed that his temperature was 103.5 degrees F., pulse rate 98, respiratory rate 22 and blood pressure 120/80. The patient appeared mildly ill. His skin was clear. The throat was diffusely red; the tonsils were not remarkable; the inguinal and axillary lymph nodes were palpable and shotty. Examination of the lungs revealed over the right middle and left lower lobes slight dullness in the percussion note, decreased fremitus, and many fine rales. The patient was admitted to the hospital with a diagnosis of pneumonia, type undetermined, after samples of sputum, blood, and nose and throat cultures had been obtained.

The laboratory studies which were immediately carried out are listed in Table VIII.*

The roentgenograms confirmed the clinical impression of pneumonia. The results of the bacteriologic studies of the blood, sputum, nasopharyngeal specimen and the clinical course ruled out a bacterial pneumonia. The morning after admission, nasopharyngeal washings were obtained immediately on awakening the patient by having him gargle with 15 ml. of a 10 per cent inactivated serum-broth mixture. These washings and triturated sputum were treated separately with penicillin to yield a final concentration of 500 units per ml. and streptomycin to yield a final concentration of 100 micrograms per ml. The resultant mixtures were permitted to stand for 30 minutes at room temperature and then used for the inoculation of white mice and of embryonated eggs by the allantoic

*The bacteriological and hematological studies, as outlined, were adopted from the tests which were employed routinely by the Pneumonia Service, Department of Medicine, the University of Rochester, and the Strong Memorial and Rochester Municipal Hospitals.

Dr. W. S. McCann, Professor of Medicine, University of Rochester School of Medicine, and Chief of the Medical Service, Strong Memorial Hospital, has fostered annually for more than 20 years a comprehensive investigative study of pneumonia. This study has provided for several house officers each year, training in the care of patients with acute infectious disease and in the clinical and laboratory development and application of successive therapeutic measures in the treatment of pneumonia. These measures over the period of years have included symptomatic treatment, specific antipneumococcal horse serum therapy, specific antipneumococcal rabbit serum therapy, sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and penicillin. Much of the author's interest and information relating to the pneumonia problem resulted from following this study over a period of 12 years. It, therefore, is a pleasure for the author to make this acknowledgement to Dr. McCann and to the successive participants in the program for the information that resulted from the study.

sac and yolk sac routes. Samples of blood which were obtained on admission and during convalescence 10 days later were set aside for serologic tests.

The mice showed no effects from inoculation. The allantoic fluid from the eggs when tested three days after inoculation was positive for hemagglutinins. Inhibition tests which were carried out with known type A and type B antisera established the virus as Influenza, type A. This conclusion was substantiated when the hemagglutinin inhibition titer of the sample of serum withdrawn 10 days after the onset of illness was found to have a 16-fold higher titer than the acute phase sample. The pneumonia, therefore, was diagnosed as Influenza, type A. Tests of the serum samples yielded no evidence for cold agglutinins or for agglutinins for *Streptococcus MG*.

Comments

The present status of our knowledge of non-bacterial pneumonias is reviewed. It is pointed out that 1) causative agents include a wide variety of organisms from protozoa to viruses; 2) the more usual pathologic, roentgenologic, and clinical pictures are essentially the same for a wide range of etiologic entities, but that variable differences occur between successive cases of the same entity and of different entities; 3) separation into etiologic entities must be accomplished by laboratory studies. Unfortunately, at present, the facilities of most diagnostic laboratories are inadequate to cope with the problem of the isolation and specific identification of viruses. For this approach, a specialized laboratory and, more particularly, specialized personnel are needed. However, the approach is simple and is in essence that which is applied for the diagnosis of a bacterial disease. Accordingly, attempts should be made to isolate the virus by utilizing materials or tissues derived from the patient, and, secondly, to identify the causative agent, when it is isolated directly or, if that is not possible, the diagnosis can be made in retrospect by assessing the patient's serum for specific antibodies. Evidence in recent years has accumulated of the successful application of present knowledge and of new developments in the field of diagnostic bacteriology and virology by the disentanglement with fair regularity of successive new entities from the "scrap pile" commonly referred to as "virus pneumonia," "interstitial pneumonia," "atypical pneumonia," or "non-bacterial pneumonia."

The general recognition that such widely different biological agents as viruses, fungi, protozoa and allergens may be the causative agent of non-bacterial pneumonia should stimulate the efforts of both the laboratorian and the clinician to direct their efforts toward making a specific diagnosis before antibiotic therapy is undertaken.

SUMMARY

In recent years, evidence has accumulated of the successful application of present knowledge and of new developments in the field of diagnostic bacteriology and virology by the disentanglement with fair regularity of successive new entities from the "scrap pile" commonly referred to as "virus pneumonia," "interstitial pneumonia," "atypical pneumonia," or "non-bacterial pneumonia." Many factors are responsible for the disentanglement and recognition of successive etiologic entities from the complex. The process has been facilitated, a) by the ready availability and common employment of chemotherapeutic and antibiotic agents for treatment, thereby eliminating effectively most bacterial agents; b) by the increasingly frequent use of roentgenography for the study of any case of suspected pneumonia; c) by the realization in hospital practice that the need is for more, rather than less, precise bacteriologic diagnosis because of the specificity of antibacterial agents and the possibility through adaptation of the appearance of resistant bacteria; and d) by the development and application of new diagnostic laboratory methods.

This review of the non-bacterial pneumonias emphasizes:

1) The importance of the non-bacterial pneumonias as a component in the complex of pulmonary infection designated clinically and pathologically as pneumonia is of recent recognition. From five to 70 per cent of all pneumonias are non-bacterial.

2) The causative agents are known to include a wide variety of microbiologic agents and their products such as viruses, rickettsia, fungi, protozoa, toxins, and allergens.

3) The more usual pathological, roentgenological, and clinical pictures are essentially the same for this wide range of etiologic entities, but variable differences occur between successive cases of the same entity and of different entities.

4) Separation into etiological entities must be accomplished by laboratory studies.

5) The facilities available in many diagnostic laboratories are inadequate to cope with the problem of the isolation and specific identification of viruses. For this approach, a specialized laboratory, and, more particularly, specialized personnel are needed. Since the approach is simple and, in essence, that which is applied for the diagnosis of a bacterial disease, attempts should be made to establish a specific diagnosis by isolation of the virus from materials or tissues derived from the patient and by its identification or, when that is not possible, to establish the diagnosis in retrospect by assessing the patient's serum for specific antibodies.

6) The general recognition that such widely different biological

agents as viruses, fungi, protozoa, and allergens may be the causative agents of non-bacterial pneumonia should stimulate the efforts of both the laboratorian and the clinician to direct their efforts toward making a specific diagnosis before antibiotic therapy is undertaken and not to be satisfied by nonspecific antibiotic "shot-gun" therapy.

RESUMEN

Recientemente se ha acumulado evidencia, usando los conocimientos presentes en el diagnóstico bacteriológico y virulógico, en la complicado cuestión de los "pneumonia a virus filtrable," "pneumonia intersticial," "pneumonia atípica" o "pneumonia abacteriana." Muchos factores son responsables en el progreso del esclarecemiento etiológico en esta materia. Este proceso fué facilitado 1) por el empleo de la quimoterapia, y antibióticos para su tratamiento, el cual elimina los agentes bacterianos; 2) por el uso frecuente y acrecentado de los rayos x, en todos los casos en que se sospecha pneumonia; 3) por la practica que se ha acrecentado mucho en los hospitales del diagnostico bacteriológico debido a la especificidad de los agentes antibacterianos, y a la posibilidad de que los bacterios se hagan resistentes; 4) por el desarrollo y aplicación de nuevos métodos de laboratorio para el diagnóstico.

Esta revista de las pneumonias no bacterianas indica:

1) La importancia de la pneumonia no bacteriana, como parte del complejo en la infeción pulmonar clinicamente y patologicamente. Desde 5 a 70 por ciento de todas las pneumonias son no bacterianas.

2) Los agentes etiológicos conocidos incluye una gran variedad de factores microbiológicos y sus productos, tales como virus, rickettsia, hongos, protozoarios, toxinas y alérgicos.

3) Los cuadros clínicos radiológico y patológico son muy semejantes en esta variedad de entidades clínicos, pero algunas diferencias pueden ocurrir en casos identicos y también en casos diferentes.

4) Por estudios de laboratorio estas entidades deben separarse etiológicamente.

5) Las facilidades de algunos laboratorios del diagnóstico, no son adecuados para resolver el problema de aislar y identificar los virus. Para esto se reguiere un laboratorio especializado y especialmente personal competente.

Desde el momento que el asunto es simple, el cual se usa para el diagnóstico de las enfermedades bacterianos, se debe hacer un esfuerzo para establecer un diagnóstico especifico, aislando el virus en el material o tejidos del paciente—y cuando esto no es posible, se puede establecer el diagnóstico retrospectivo identificando los anticuerpos específicos en el suero del enfermo.

6) El reconocimiento general que tales agentes biológicos, tan diferentes como virus, hongos, protozoarios y alérgicos, pueden ser los causantes de la pneumonia no bacteriana, deberia estimular los esfuerzos del laboratorista y del clinico para hacer un diagnóstico espécifico, antes de iniciar el tratamiento con los antibioticos y no quedarse satisfecho con un tratamiento de antibioticos que no es especifico, como seria un "Tiro de escopeta."

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Medical Management of Acute Lung Abscess
Report of 12 Cases*

JIM S. JEWETT, M.D. and GEORGE E. DIMOND, M.D.
Dearborn, Michigan

Within the past decade, the medical regimen for lung abscess has included postural drainage, bronchoscopic aspiration and irrigation, artificial pneumothorax, intravenous injections of arsphenamine and guaiacol, rectal instillations of ether in oil, and the oral administration of potassium iodide and sulfonamides. The data reported by Rosenblatt (1940)[1] indicate the hazards and ineffectiveness of such treatment. Of 72 patients with putrid lung abscess treated medically, only 9 per cent were improved or cured, and 91 per cent were either unimproved or dead.

Allen and Blackman[2] in 1936 collected 2,114 cases of pulmonary abscess from the American literature and found the mortality with medical treatment was 34.4 per cent, and with both medical and surgical treatment was 34.2 per cent. In 1948, Smith[3] published a statistical analysis of 2,166 cases compiled by representative hospitals throughout this country from 1936 to 1944 and concluded that no material change in the gross mortality (34.2 per cent) had occurred.

With the addition of penicillin an appreciable increase in the number of symptomatic cures of medically treated lung abscess has been reported. Potter,[4] however, questions that the follow-up of these cases has been sufficiently long to determine whether spontaneous obliteration of abscess cavities has materially increased.

Material

During a 24 months period we have observed 28 cases of lung abscess (Table 1). Eleven cases are reported in which acute suppuration occurred in a previously healthy lung, as distinguished from suppuration secondary to malignancies, bronchiectasis and cystic lung disease. One additional case of acute abscess in a bronchiectatic lobe is included because complete healing of the abscess cavity resulted under medical management. One case of amebic lung abscess with bronchopleural fistula was successfully

*From the Department of Medicine, Wayne University College of Medicine, and the Veterans Administration Hospital, Dearborn, Michigan. Published with permission of the Chief Medical Director, Veterans Administration. Department of Medicine and Surgery, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

treated without surgical drainage. One fatality occurred, following spontaneous evacuation of a giant abscess into the pleural space, despite immediate surgical drainage.

Report of Cases

Case 1: W.B., a 49 year old laborer, was admitted on December 21, 1947 with a five weeks' history of chills and fever, productive cough, hemoptysis, dyspnea, and a 35 pound weight loss. He was orthopneic, hoarse, and seriously ill. The temperature was 102.4 degrees F. He coughed up large amounts of fetid, blood streaked pus. There were diminished reson-

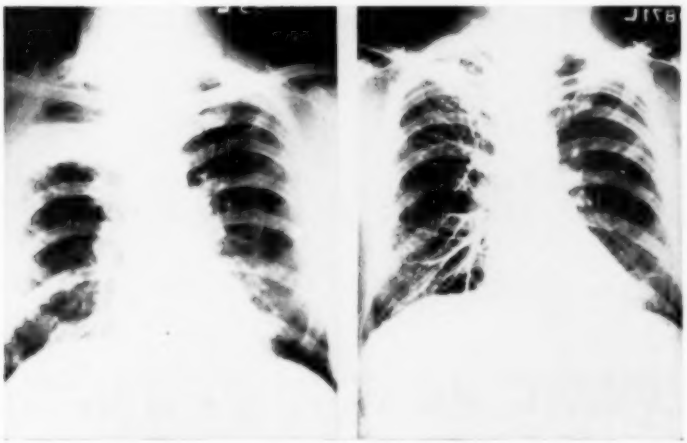

FIGURE 1a FIGURE 1b

Fig. 1 (Case 1): (a) Large abscess cavity with fluid level in right upper lobe. (b) Complete clearing after 54 days of penicillin therapy and normal bronchogram 14 months later.

TABLE 1

Types of Lung Abscess Observed

Primary:	
Acute	10
Chronic	2
Amebic	1
Secondary:	
Bronchogenic Carcinoma	7
Bronchiectasis	6
Reticuloendotheliosis	1
Cystic Lung Disease	1
TOTAL	28

TABLE 2

Summary of Penicillin Dosage and Results of Therapy

Case No.	Age, Race	Location of Lesion	PENICILLIN — Intramuscularly Dosage	Days	PENICILLIN — Aerosol Dosage	Days	AFTER THERAPY BEGUN — Fever Subsided	Abscess Cavity Lost to View
1	49 W	RUL	D* 320,000	34	90,000 120,000	15 33	20 days	54 days
			T* 10,880,000	34	3,960,000	48		
2	49 W	LLL	400,000 240,000	15 27	80,000	14	1 day	42 days
			12,480,000	42	1,120,000	14		
3	31 W	LUL	400,000	12	300,000 200,000	14 18	5 days	31 days
			4,800,000	12	7,800,000	32		
4	28 N	RUL	300,000 400,000	37 64	200,000	70	7 days	82 days
			36,700,000	101	14,000,000	70		
5	48 N	RLL LUL	240,000	41	270,000 120,000	18 41	25 days	50 days
			9,840,000	41	9,780,000	59		
6	52 W	RUL	320,000	78	200,000	60	afebrile	residual bronchiectasis
			24,960,000	78	12,000,000	60		

Case No.	Age, Race	Location of Lesion	— — — PENICILLIN — — — Intramuscularly Dosage	Days	Aerosol Dosage	Days	— AFTER THERAPY BEGUN — Fever Subsided	Abscess Cavity Lost to View
7	44 W	RUL	240,000 300,000	17 37	400,000 200,000	14 37	7 days	41 days
			15,180,000	54	13,000,000	51		
8	58 W	LUL	400,000 300,000	40 24	300,000 150,000	64 25	5 days	30 days
			23,200,000	64	22,950,000	89		
9	33 N	LLL	400,000 300,000	22 16	200,000	38	5 days	35 days
			13,600,000	38	7,600,000	38		
10	45 W	RUL	400,000	47	200,000	105	14 days	100 days
			18,800,000	47	21,000,000	105		
11	53 W	RUL	320,000 640,000 800,000	4 4 30	280,000	8	Expired on 38th day	
			27,840,000	38	2,240,000	8		
12	31 W	RLL	240,000 300,000 400,000	9 7 24	200,000	25	7 days	55 days
			13,860,000	50	5,000,000	25		
D* Daily dosage. T* Total dosage and days.					Average		9 days	52 days

ance, bronchial breathing, and rales over the upper lobe of the right lung. Carious teeth and oral sepsis were noted.

On the chest roentgenogram a large abscess cavity (8 cm. in diameter) with a moderately thick wall (1 cm.) was demonstrated in the right apex. The erythrocyte count was 2.7 million. The leukocyte count was 12,400. Streptococcus viridans predominated on aerobic cultures of the sputa.

Parenteral penicillin was begun immediately but was interrupted for 10 days because the process was mistakenly thought to be tuberculous. In the interval a fluid level developed in the abscess cavity (Fig. 1). On bronchoscopic examination pus was draining from a patent right upper lobe orifice. The vocal cords were edematous. Despite the subsidence of fever and amelioration of symptoms after three weeks of therapy, the lack of improvement by roentgenogram prompted his transfer to the surgical service for pneumonotomy. On a preoperative roentgenogram some decrease in the size of the cavity was first noted and surgery was deferred. Thereafter progressive clearing of the abscess was observed. After 54 days the cavity was no longer visible.

He was discharged April 23. (See Table 2 for a summary of penicillin dosage). A normal chest roentgenogram and bronchogram of the right lung were obtained 14 months later (Fig. 1). This patient has been followed 22 months and has remained well.

Comment: When cavitary pulmonary tuberculosis is suspected and the sputum is abundant, the inability to demonstrate tubercle bacilli on direct smear or in concentrates should suggest an early revision of the diagnosis. Penicillin therapy of suspected lung abscess should not be delayed while attempting to exclude tuberculosis. Valuable time was lost and this patient's lesion was in excess of two months duration before penicillin therapy was begun. Despite this delay and the thickened wall noted on the roentgenogram, complete resolution occurred.

Case 2: D.B., a 49 year old carpenter, expectorated a cupful of malodorous, thick, green pus following a paroxysm of coughing on February 15, 1948 and was hospitalized two days later. A weight loss of 20 pounds had occurred during the preceding six weeks. For five days prior to admission he had intermittent chills and fever, pain in the left side of chest, severe headaches and loss of appetite. He was irrational and seriously ill. The breath was fetid and his cough was profusely productive. The temperature was 101.2 degrees F., the pulse was 124 per minute, and the respirations were 32 per minute.

The chest roentgenogram (Fig. 2) disclosed an abscess with a fluid level in the superior segment of the left lower lobe. There was a leukocytosis (15,950 cells). Streptococcus viridans and streptococcus beta hemolyticus were cultured from the sputum. The spinal fluid was normal.

Parenteral penicillin therapy was begun on admission. The temperature returned to normal within 24 hours and the volume of sputum promptly decreased from 600 cc. to 50 cc. per 24 hour period. The only abnormality seen on bronchoscopic examination was hyperemia of the left main stem bronchus. After 42 days the abscess cavity was lost to view. He was discharged on April 16.

A follow-up chest roentgenogram and bronchogram of the left lower

lobe were within normal limits 14 months later (Fig. 2). It has been 21 months since complete resolution of the abscess cavity, without evidence of recurrence.

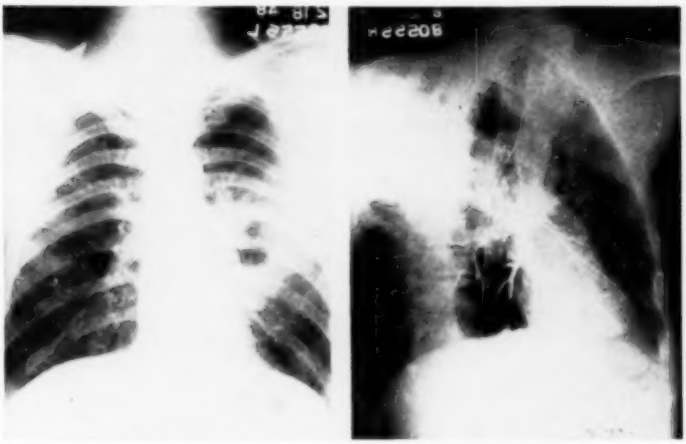

FIGURE 2a FIGURE 2b

Fig. 2 (Case 2): (a) Abscess in superior segment of the left lower lobe. (b) Complete clearing after 42 days of penicillin therapy and normal bronchogram 14 months later.

Comment: Metastatic brain abscess was considered at the time of admission but was not confirmed. Embolic brain abscess with fatal outcome is not an infrequent complication of pulmonary suppuration, and should be considered when headache or mental confusion are prominent symptoms. Seven of the 10 metastatic brain abscesses successfully treated by Rizzoli and co-workers were considered thoracogenic.[5]

Case 3: J.F., a 31 year old metal grinder, was admitted on March 20, 1948 with a history of cough, profusely productive of foul smelling sputum, chills, fever, chest pain, anorexia, and profound prostration of one week's duration. The past history included bronchial asthma and two episodes of pneumonia in childhood. The breath was fetid. He coughed frequently and expectorated foul smelling, thick, blood streaked pus. The temperature was 101.4 degrees F., the pulse was 124 per minute, and the respirations were 28 per minute. The teeth were markedly carious.

The chest roentgenogram revealed an abscess cavity in the subapical segment of the left upper lobe with an air fluid level and extensive perifocal reaction (Fig. 3). The leukocyte count was 19,250. Hemolytic staphylococcus albus predominated on aerobic cultures of the sputa.

Penicillin was administered intramuscularly from the day of admission and on the second hospital day sulfonamides and penicillin aerosol were added. The aerosolized penicillin was preceded by one half cc. of nebulized "Vaponefrin" (2.25 per cent solution of racemic epinephrine) dur-

ing waking hours. The volume of sputum markedly diminished and he became afebrile on the fifth hospital day. After 31 days of therapy, the cavity was no longer visible. He was discharged April 22 asymptomatic and with a 20 pound weight gain.

Chest roentgenogram 21 months later was normal. A bronchogram revealed the bronchial radicals of the left upper lobe to be entirely normal, but far advanced cylindrical bronchiectasis was demonstrated in the basilar segments of the left lower lobe (Fig. 3).

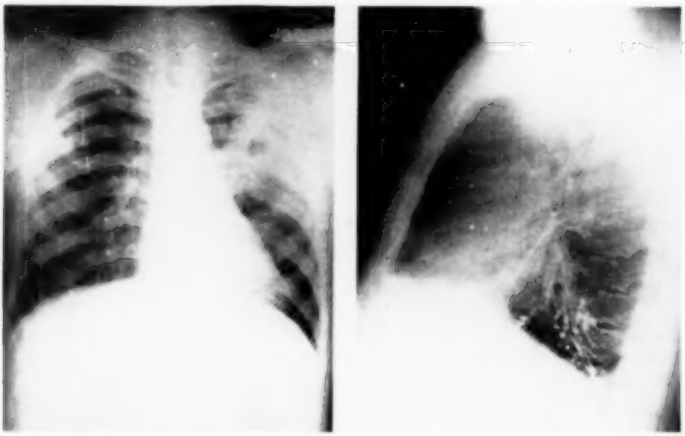

FIGURE 3a FIGURE 3b

Fig. 3 (Case 3): (a) Abscess cavity with marked perifocal reaction in subapical segment of the left upper lobe. (b) Complete clearing after 31 days of penicillin therapy, but bronchogram 21 months later shows bronchiectasis in the basilar segments of the left lower lobe.

Comment: The abscess in the subapical segment of the left upper lobe was considered incident to gravity spillage from a long standing lower lobe bronchiectasis. Because of the known bronchodilator effect of epinephrine-like substances administered by nebulization in asthmatics,[6] these should facilitate the transmission of aerosolized penicillin through the terminal bronchioles.

Case 4: J.S., a 28 year old college student, following a mild infection of the upper respiratory tract in April of 1948, had a sudden onset of chills and fever to 103 degrees F., pain in the right side of the chest, and a cough productive of foul, bloody sputum. The third week of his illness a chest roentgenogram obtained elsewhere was interpreted as lung abscess of the right upper lobe. His family physician had administered 300,000 units of penicillin in oil and wax in a single intramuscular injection daily for approximately one month prior to his admission here on June 22. Subsidence of fever and clinical improvement had been noted after one week of therapy. When first seen here he was chronically ill, but was afebrile. There had been a 25 pound weight loss. There were rhonchi over the right upper hemithorax. Oral sepsis was present.

The chest roentgenogram showed an area of infiltration containing several small cavities in the subapical segment of the right upper lobe. Beta hemolytic streptococci predominated on aerobic cultures of the sputa. Penicillin was administered intramuscularly and by aerosolization from the day of admission. Serial roentgenograms showed progressive clearing of the lesion and after 82 days only minimal fibrosis remained. A bronchogram showed no evidence of dilatation or obstruction of the bronchial radicals. Medication was discontinued on August 31, and he was discharged asymptomatic. The chest roentgenogram one year later was read as negative. Over 17 months have now elapsed with no evidence of recurrence.

Comment: This patient received over 50 million units of penicillin in a course extending over a period of 101 days. Although he became afebrile at the end of one week, complete clearing of the lesion did not result until after 82 days of therapy.

Case 5: A.W., a 48 year old Negro was transferred to the medical chest service on July 29, 1948 for the treatment of an acute putrid abscess of the upper lobe of the left lung, resulting from suppuration in a bland pulmonary infarction. He was admitted on December 26, 1947 to the cardiac service with a history of progressive exertional dyspnea, angina pectoris, and high blood pressure since 1940. The occupational history included coal mining for a number of years. The chest roentgenogram on admission was consistent with pneumonoconiosis. The electrocardiogram was diagnostic of a recent anteroseptal myocardial infarction. In February lateral extension of the myocardial infarction was demonstrated on the electrocardiogram.

In April there was a sudden onset of pleural pain in the right side of

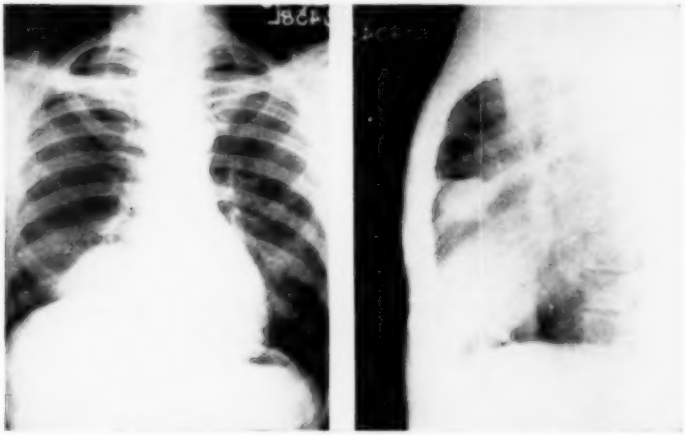

FIGURE 4a FIGURE 4b

Fig. 4 (Case 5): Abscess in (a) right lower lobe and (b) pectoral segment of left upper lobe incident to pulmonary infarction. Both cleared completely with penicillin therapy.

the chest, followed by fever and cough markedly productive of foul, blood streaked, coal black sputum. A rounded density was noted on the roentgenogram in the base of the right lung (Fig. 4). A clinical diagnosis of pulmonary infarction with suppurative breakdown was entertained. Penicillin was administered intramuscularly, with prompt subsidence of fever in the ensuing week, and was then discontinued. He was given supportive treatment with gradual clinical and roentgenologic improvement until July 2, when he again spiked a fever to 101 degrees F. and complained of severe pain in the left side of the chest. The cough became increasingly productive of foul, blood streaked, black, tenacious sputum. Penicillin therapy was reinstituted on July 6. On July 16, the chest roentgenogram showed elevation of the left leaf of the diaphragm and a large abscess cavity with fluid level in the pectoral segment of the left upper lobe (Fig. 4). The leukocyte count was 13,500. On bronchoscopic examination pus was seen in the left upper lobe bronchus. Following his transfer to the chest ward, penicillin aerosol and sulfonamides were added to the regimen. The fever subsided after 25 days. The abscess was no longer visible by August 25.

At the time of discharge on September 29, the only abnormality noted on the chest roentgenogram was extensive interstitial nodular infiltration throughout both lungs, such as described on the initial film.

Comment: Chester and Krause[7] have emphasized that pulmonary infarction should be considered as a possible underlying cause in every case of lung abscess, especially if cardiac failure is present. An antemortum diagnosis of abscess secondary to bland pulmonary infarction was definitely established in only three of 23 cases collected by Levin et al[8] among 550 necropsies in which infarcts were found. Of the 23 cases in which suppurative breakdown occurred in a bland pulmonary infarction, 15 were nonoperative pulmonary infarctions, and of the latter cardiac decompensation was present in 13. It is suggested by Levin that abscess formation should be suspected in any case of pulmonary infarction in which leukocytosis, unremitting fever, and possibly a productive cough subsequently develop.

Case 6: O.K., a 52 year old alcoholic addict, was admitted to the isolation section on August 12, 1948 with a three weeks' history of productive cough, fetid breath, hemoptysis, 20 pound weight loss, and prostration. Chills, fever, and chest pain were denied. He appeared malnourished, anemic, and chronically ill. Fever was notably absent. There were physical signs of consolidation extending from the second to the sixth rib posteriorly on the right. The liver was enlarged and tender. Finger clubbing was noted.

The chest roentgenogram (Fig. 5) showed a rather homogeneous density obscuring the right upper lobe. Several cavities were noted in this area, at least one of which contained an air fluid level. The trachea was deviated to the side of the lesion, and emphysematous changes were present throughout the aerated lung. The erythrocyte count was 3.4 million with 10.5 grams of hemoglobin. The leukocyte count and differential formula were normal. The 5 mg. per kg. bromsulphthalein test showed a 30 per cent retention of the dye at 45 minutes. The sputa were examined

for tubercle bacilli but none were found. No intrinsic lesion of the bronchus was demonstrated on bronchoscopic examination. No neoplastic cells were identified in bronchial aspirations.

General supportive therapy was given during a three weeks period of observation without improvement. Following his transfer to the medical chest service, penicillin was administered intramuscularly and by aerosolization. The sputum decreased after one week. Serial roentgenograms showed progressive clearing of the infiltration, but the cystic changes persisted. These cyst-like cavities in the right upper lobe, filled with iodized oil on a bronchogram October 21 (Fig. 5). He was discharged December 17, asymptomatic. The erythrocyte count and hemoglobin, as well as liver function tests were all within normal limits. He has remained well for over one year.

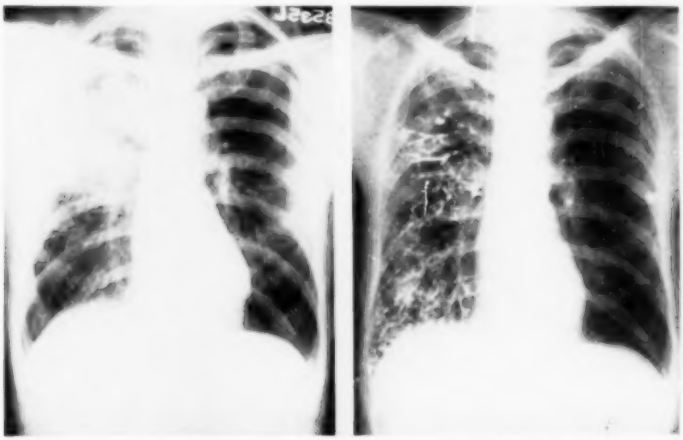

FIGURE 5a FIGURE 5b

Fig. 5 (Case 6): (a) Multilocular abscess of the right upper lobe. (b) Infiltration cleared during penicillin therapy but bronchogram shows residual bronchiectasis.

Comment: As in Case 1, penicillin therapy was needlessly delayed during a three weeks' period of observation for tuberculosis. It is assumed that the bronchiectasis represents a complication of the abscess, rather than the converse. Because of the pulmonary emphysema the thoracic surgeons elected to defer lobectomy as long as he remained asymptomatic. The lack of chills, fever, and chest pain are unusual.

Case 7: H.C., a 44 year old steamfitter, was admitted on January 22, 1949 with a history of chills, fever, pain in the right side of the chest, cough productive of bloody, purulent sputum, and prostration of two days' duration. His temperature was 104 degrees F. There were oral sepsis and physical signs of consolidation of the upper lobe of the right lung.

An infiltration with an area of rarefaction 2 cm. in diameter was noted

on the chest roentgenogram in the pectoral segment of the right upper lobe. An examination three days later showed an extension of the lesion at which time the rarefaction measured 4 cm. in diameter.

Penicillin was administered intramuscularly from the day of admission and three days later penicillin aerosol was added. On the fifth hospital day he was still spiking a fever to 103 degrees F. At this juncture, because of the apparent lack of response to penicillin, sulfadiazine was added. Two days later the temperature fell to normal, and there was striking clinical improvement. No significant abnormalities were noted on bronchoscopic examination. The abscess cavity was no longer visible after 6 weeks. On March 8, the right lung was mapped with iodized oil. No defects in the bronchi were demonstrated.

He was discharged asymptomatic on March 17, and advised to continue on penicillin aerosol for a period of one month at home. In July 1948, the chest roentgenogram revealed minimal scarring in the right mid-lung field, but was otherwise within normal limits. Ten months following discharge there has been no evidence of recurrence.

Comment: This patient received penicillin for five days with no apparent response. Two days after sulfadiazine was added his temperature fell to normal with striking clinical improvement. Although one is tempted to give sulfadiazine a share of the credit, we have observed a similar course where sulfonamides were not employed; i.e., a clinical response to penicillin did not occur in less than one week.

Case 8: J.T., a 58 year old foundry worker, had an onset of harassing, non-productive cough in November, 1948, which became progressively worse. In January, 1949 a severe aching pain developed in the left side of the chest. Chills and fever recurred daily. The cough became productive of large amounts of foul purulent sputum. There was a precipitous weight loss of 65 pounds. He was admitted on January 31, 1949, moribund. Cachexia was extreme. His height was 71 inches (180.3 cm.) and he weighed 90 pounds (40.8 kg.). The temperature was 101 degrees F., the pulse was 100 per minute, and the respirations were 24 per minute. There was obvious pulmonary emphysema. Crepitant rales were heard over the left lower anterior aspect of the chest.

A large, irregularly outlined, rounded density 8.0 cm. in diameter was present on the roentgenogram in the lingula of the left upper lobe (Fig. 6). Several small cystic or cavernous areas were noted within this density. There was a leukocytosis (15,850 cells) and a left shift of the differential formula. The hemoglobin was 12.5 grams. Preparations of the sputa, using Papanicoloau's technique, were negative, Class 1. Two bronchoscopic examinations were essentially normal except for the presence of pus in the left main stem bronchus.

Penicillin therapy was begun on the second hospital day, administered both intramuscularly and by aerosolization. The temperature fell to normal on the fifth day of therapy, and marked clinical improvement occurred. After 30 days only a stellate scar remained. A bronchogram March 8, showed no evidence of obstruction or dilatation of the major bronchi (Fig. 6).

He was discharged on May 2, asymptomatic, having gained 44 pounds

in weight. He was advised to continue the aerosol penicillin at home for an additional month. There has been no evidence of recurrence nine months since discharge.

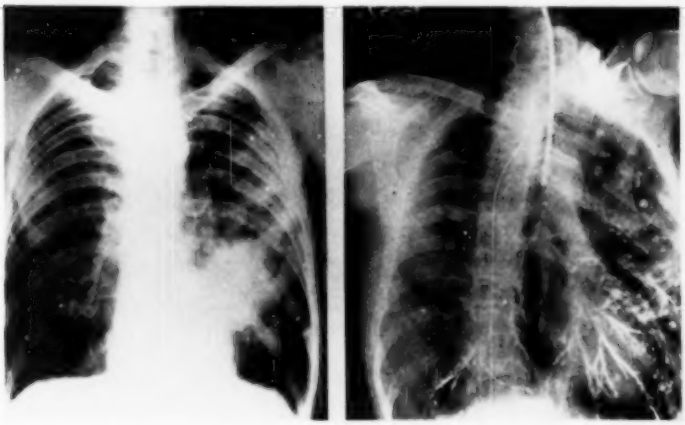

FIGURE 6a FIGURE 6b

Fig. 6 (Case 8): (a) Abscess in lingula of left upper lobe. (b) Complete clearing after 30 days of penicillin therapy and normal bronchogram.

Comment: On admission this patient presented the picture of a far advanced bronchogenic carcinoma with suppuration behind an obstructed bronchus. In spite of his rapid deterioration prior to therapy complete recovery resulted.

Case 9: P.P., a 33 year old lathe operator, was admitted on May 11, 1949, complaining of a productive cough, associated with fever, chills, night-sweats, weakness, and a 15 pound weight loss over the preceding three weeks. The day preceding admission the cough suddenly became productive of large quantities of green sputum. Significant in the past history were an episode of hemoptysis in 1943 and chronic productive cough in the intervening years. On admission the temperature was 104 degrees F., the pulse was 110 per minute, and the respirations were 20 per minute. Crackling rales were heard at the base of the left lung.

A chest roentgenogram showed a cavity 5 cm. in diameter with an air fluid level in the lateral basilar segment of the left lower lobe (Fig. 7). The leukocyte count was 21,550. The hemoglobin was 11 grams. Beta hemolytic streptococci and pneumococci predominated on aerobic culture of the sputum.

Penicillin was administered from the day of admission both intramuscularly and by aerosol. He became afebrile the fifth hospital day. The abscess cavity was lost to view on the 35th day of therapy. On July 7, bronchial mapping of both lungs revealed evidence of advanced cylindrical bronchiectasis and contraction of the left lower lobe (Fig. 7). On August 17, 1949, left lower lobectomy was performed. The inferior lateral

aspect of the lobe on cut section showed an area of increased fibrosis, but no abscess cavity could be identified. His postoperative course was uneventful. He was discharged on September 13.

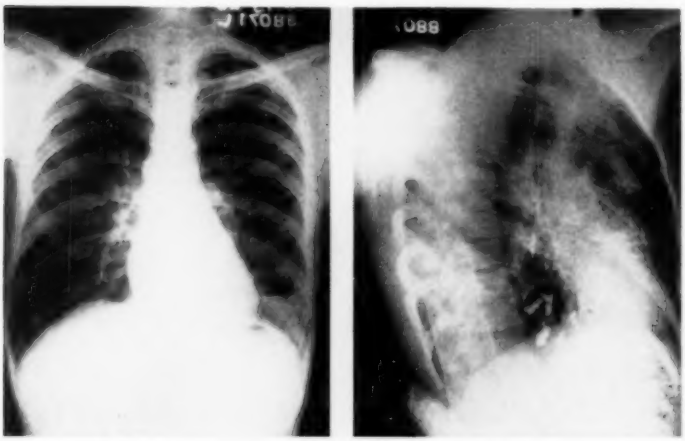

FIGURE 7a FIGURE 7b

Fig. 7 (Case 9): (a) Abscess cavity with fluid level in lateral basilar segment of left lower lobe. (b) Complete clearing after 35 days of penicillin therapy, but bronchogram shows far advanced cylindrical bronchiectasis and contraction of the left lower lobe.

Comment: The history would indicate that bronchiectasis unquestionably antedated the abscess. It is of interest that complete healing of the lung abscess was demonstrated in the surgical specimen.

Case 10: E.V.V., a 45 year old truck driver, had an acute onset of fever, productive cough, sharp pleuritic chest pain, accompanied by anorexia and severe prostration 10 days preceding admission on May 23, 1949. For two years he had had a cough and had noted weakness, ease of fatigue and a decrement in weight of 30 pounds. He was pallid and emaciated, weighing 100 pounds (45.4 kg). The temperature was 101.6 degrees F., the pulse was 120, and respirations were 20 per minute. The chest was emphysematous. There were an inspiratory lag on the right and physical signs of consolidation of the upper lobe of the right lung.

The chest roentgenogram showed a dense infiltration with "honey combing" of the right upper lobe (Fig. 8). There was extensive emphysema of the remaining lung fields. The leukocyte count was 32,000, with 81 per cent neutrophils. The hemoglobin was 9 grams, with 2.9 million erythrocytes. The sputum cultures grew the usual mouth organisms. Slight retraction of the trachea to the right, but without fixation, was noted on bronchoscopic examination. Bronchial secretions for cytologic examination were obtained from the right upper lobe bronchial orifice, and were interpreted as negative, Class 1.

Penicillin was administered intramuscularly from the day of admission. By the fifth hospital day he continued to spike a fever to 102 degrees F. daily and aerosol penicillin was added. A high caloric, high vitamin alimentation was given together with whole blood transfusions. On the ninth hospital day the fever began to fall by lysis and he became afebrile five days later. There was a 15 pounds weight gain within one month. After 100 days only a slight density remained in the apex. A bronchogram revealed some crowding of the more terminal radicals of the apical and subapical branches of the right upper lobe bronchus (Fig. 8). These changes were considered incident to pulmonary fibrosis. He was discharged asymptomatic after 109 hospital days, having gained 27 pounds in weight. He was advised to continue penicillin aerosol therapy at home for 30 days.

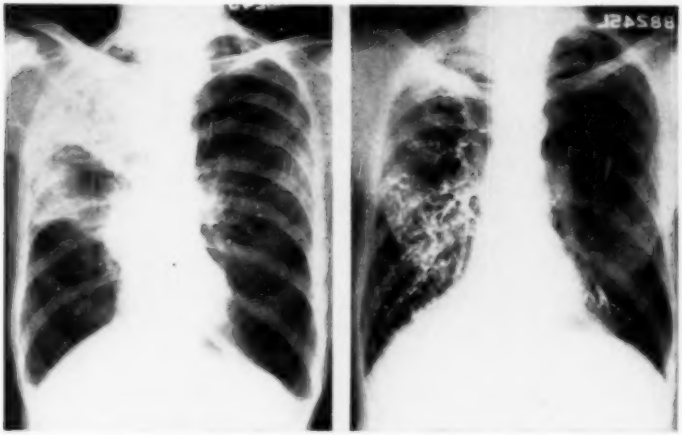

FIGURE 8a FIGURE 8b

Fig. 8 (Case 10): (a) Multilocular abscess of right upper lobe. (b) Only small scar remained after 100 days of penicillin therapy and bronchogram essentially negative.

Comment: The history and the character of the sputum were considered more in keeping with pulmonary tuberculosis, or bronchogenic carcinoma than lung abscess. The leukocytosis of 32,000 and the failure to demonstrate tubercle bacilli in the sputum, however, did not support that impression. The clinical course confirmed the diagnosis of lung abscess. The abnormalities noted on the bronchogram may remain stationary, but bronchiectasis may eventuate.

Case 11: E.C., a 53 year old Italian laborer, was struck in the chest with a 100 pound sack of potatoes while working at a produce market and was admitted three weeks later on September 27, 1949. During the week preceding admission his illness was characterized by chills and fever, dyspnea, copious expectoration of foul, bloody sputum and marked prostra-

tion. His lips were cyanotic, the breath was fetid, and respirations were noisy and rapid. The temperature was 101.6 degrees F., the respirations were 36 per minute, and the pulse was 100 per minute. There were an inspiratory lag, diminished expansion and impaired resonance of the right hemithorax. The abdomen was distended and tympanitic. The liver was enlarged.

The chest roentgenogram revealed a large cavity with an air fluid level in the upper lobe of the right lung, with a moderate collection of pleural fluid at the right base (Fig. 9). The leukocyte count was 23,500 with a left shift of the differential formula.

FIGURE 9a FIGURE 9b

Fig. 9 (Case 11): (a) Giant abscess cavity with fluid level presumably in right upper lobe. (b) Spontaneous evacuation into the pleural space with resultant pyopneumothorax.

Penicillin was administered from the day of admission intramuscularly and by aerosolization. A sulfadiazine-sulfathiazole mixture was also employed, but, because of the early appearance of heavy crystalluria, was discontinued after three days. On the seventh hospital day he became psychotic and delirious. A brain abscess was suspected but there were no localizing signs. The spinal fluid dynamics and constituents were within normal limits. The leukocyte count markedly increased (40,950 cells with 90 per cent polymorphonuclears). Roentgenogram showed the abscess had evacuated and a considerable increase in the pleural collection of fluid at the right base had occurred (Fig. 9). An emergency thoracotomy was performed under local anesthesia, and a large amount of foul pus was evacuated. A No. 32 Pezzar catheter was inserted through the thoracotomy wound and attached to a water-seal, gravity drainage. Immediately postoperative he became cyanotic, comatose and moribund. General supportive treatment was given with temporary improvement. His course was one of progressive deterioration with the subsequent appearance of jaundice, anasarca, ascites and ileus. The treatment included penicillin, digitalization, mercurial diuretics, gastric intubation for de-

compression, multiple transfusions and repeated bronchoscopic aspirations. A sulfathiazole-sulfadiazine mixture was again administered as well as streptomycin. He remained febrile and expired the 38th hospital day. Permission for necropsy was not granted.

Comment: This patient received both medical and surgical therapy and was the only case in which spontaneous rupture of an abscess into the pleural space occurred. Such a catastrophe might have been prevented by early pneumonotomy. In spite of emergency thoracotomy and adequate evacuation of the pyothorax his course was one of gradual deterioration. The history of chest trauma two weeks preceding onset of symptoms suggests that a contusion of the lung may have occurred which ultimately went on to suppuration and abscess formation.

Case 12: C.B., a 31 year old World War II veteran of the South Pacific Theater, was hospitalized here initially in September 1946, at which time an amebic abscess of the liver was drained and he received a course of emetine totalling 11½ grains. He remained well until the spring of 1948 when he again observed transient pain in the right side of the chest and progressive fatigue. Four months prior to his second admission, December 11, 1948, his appetite began to fail and he lost weight. Chills and fever recurred daily. Chest pain and prostration were progressive. Cough with abundant expectoration of foul bloody sputum developed. For a few weeks prior to admission dyspnea had been distressing on slight exertion. The temperature was 102 degrees F., the pulse was 120 per minute, and respirations were 36 per minute. The cough was profusely productive of "tomato catsup-like" sputum. There was moderate pallor and weight loss.

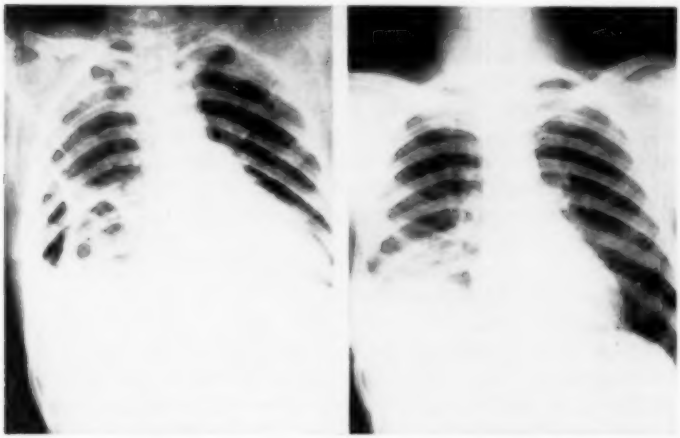

FIGURE 10a FIGURE 10b

Fig. 10 (Case 12): (a) Large abscess cavity in right lower lobe with bronchopleural fistula. (b) Abscess cavity no longer visible, but residual tenting of diaphragm and pleural reaction are present.

The right hemithorax was splinted and breath sounds were diminished. Moist rales were heard at the inferior tip of the right scapula.

On the chest roentgenogram a large cavity with an air fluid level was seen in the right lower lung field. A second density was noted in the right costophrenic angle with an air fluid level suggesting a bronchopleural fistula (Fig. 10). The leukocyte count was 28,100 and hemoglobin was 8.2 grams. The albumin-globulin ratio was reversed. Endamoeba histolytica cysts were recovered in the stool. The complement fixation titer for amebiasis was positive in a dilution of 1:128. The sputum was repeatedly examined for amebae on direct smear with saline and iodine but none were seen. Aerobic and anaerobic cultures of the sputum for amebae were likewise negative. On thoracentesis a reddish-brown material identical to the material expectorated was recovered.

A diagnosis of amebic lung abscess with bronchopleural fistula and pyopneumothorax secondary to a recurrence of liver abscess was made. Therapy consisted of repeated pleural aspirations, penicillin and amebacides, together with general supportive measures. Penicillin was administered intramuscularly from the day of admission, and later by aerosolization. He received two courses of emetine hydrochloride 1 gr. daily for 10 days and two courses of diodoquin 9.6 gr. t.i.d., for 21 days with suitable intervening rest periods. Multiple whole blood transfusions were given. He became afebrile on the seventh hospital day. The final roentgenogram the day of discharge, February 4, showed some residual pleural thickening and tenting of the right leaf of the diaphragm. The abscess cavity was no longer visible (Fig. 10). He has been asymptomatic for a period of one year.

Comment: Ochsner and DeBakey[9] have estimated that about 15 per cent of patients having amebic hepatitis (or abscess) have pleuropulmonary complications. Koszalka[10] considers wide thoracotomy mandatory if a liver abscess ruptures through the diaphragm. This patient was seen in consultation by the thoracic surgeons, and it was agreed to defer thoracotomy as long as clinical improvement continued under repeated thoracentesis. It is well recognized that several courses of systemic and intestinal amebacides are frequently necessary to eradicate the infection. Had such a course been followed during this patient's first admission, a recurrence might have been avoided.

Discussion

The management of acute uncomplicated lung abscess has been modified in the past few years. With the knowledge that rapid healing can occur with penicillin, the pendulum has swung away from early pneumonotomy in favor of antibiotic therapy. Adequate drainage is axiomatic in the treatment of any localized collection of pus, but due to the bronchial communication of pulmonary abscess, internal drainage may suffice.

A needless controversy still exists between the proponents of early intensive medical management and those favoring early

surgical intervention precluding a trial of medical therapy. There need be no competition between medicine and surgery. Samson[11] has emphasized that pulmonary abscess is a serious and unpredictable disease with ever present surgical potentialities, and has urged frequent consultations between the internist and his thoracic surgical consultant.

It is now clear that a high recovery rate cannot be anticipated if all acute lung abscesses be surgically drained. Touroff and Neuhof,[12] have found surgical intervention generally of no value in the management of acute uncomplicated nonputrid abscess, and they feel moreover that in many cases it may be absolutely harmful.

Maxwell[13a] (1934) proposed six factors upon which he felt therapy depended:

1) The cause of the abscess.
2) The duration of the abscess.
3) The general condition of the patient.
4) The nature and virulence of the infecting organism.
5) The site and extent of the lesion.
6) The presence of complications in the lung and pleura.

These same criteria may be applied equally well today.

1) *The Cause of the Abscess:* The etiology and precipitating factors of lung abscess have been adequately discussed in the literature.[3,13a,b,c,d] Bronchoscopic examination, early in the course of the disease, serves as a safeguard against an unnecessary delay in arriving at a diagnosis of neoplasm (present in 25 per cent of our series, Table 1) or rarely a foreign body. In addition, internal drainage may be facilitated. The examination should include aspiration of secretions for bacteriologic and cytologic study.

2) *The Duration of the Abscess:* It is now generally accepted that the onset should be figured from the first appearance of fever and signs of pulmonary infection, and need not coincide with the production of characteristic sputum and roentgenographic evidence of excavation. It has been emphasized by Smith[3] and others that lung abscesses respond best to medical management when treatment is begun within six weeks of onset. Whereas Bailey[14] considers abscesses acute if less than two months' duration, there is no disagreement with regard to the urgency for early recognition and treatment.

Only acute lung abscesses, those in which symptoms have been present for two months or less, are considered good subjects for medical management. There is now general agreement that no abscess is doing well that remains unchanged on the roentgenogram for two to three weeks at a time, even if there has been amelioration of symptoms. This is considered an indication for external drainage, or resection.

3) *General Condition of the Patient:* Supportive treatment differs in no essential respects from that of any severe pulmonary infection. The patient should be turned in bed so that coughing is induced, but heroic efforts at postural drainage are seldom justified. Narcotics should be used sparingly.

4) *The Nature and Virulence of the Infecting Organisms:* Potter[4] has expressed the opinion that the clinical course is a more practical measure of bacterial sensitivity or resistance to penicillin than extensive bacteriologic studies. Recent emphasis on bacterologic diagnosis and in vitro sensitivity has resulted from the introduction of a group of newer antibiotics.

5) *The Site and Extent of the Lesion:* The exact anatomical location of the lesion with reference to lobes and segments can best be determined by fluoroscopic inspection and by suitable roentgenograms. A knowledge of pulmonary topography and bronchopulmonary segmental anatomy is necessary for accurate localization. We have used Brock's[15] terminology. If an interlobar empyema is mistaken for a lung abscess surgical drainage may be unnecessarily delayed. Brock states that fully 50 per cent of cases of lung abscess do not show convincing evidence of cavitation on radiograms. Among the 23 cases of lung abscess reviewed by Levin,[8] there was roentgenologic evidence of abscess in only three.

6) *The Presence of Complications in the Lungs and Pleura:* In conclusion, the diagnosis must include any local or distant extension of the process. Rupture into the pleural space is an indication for prompt surgical intervention. Spreads to adjacent lobes and mediastinal structures, are accompanied by increased morbidity and mortality. Septicopyemia and brain abscess frequently terminate fatally.

Bronchographic follow-up of patients treated by both surgical and medical means reveals that a small but significant number are left with residual parenchymal and bronchiectatic changes. If symptoms persist as a result of these sequelae medical management should be supplemented with surgery. Kay and Meade[16] have reported a mortality of 1 per cent in a series of 100 cases of chronic suppurative disease subjected to lobectomy.

Penicillin Therapy

Until penicillin was made generally available the mortality, regardless of the method of management, remained practically unchanged, as attested by several comprehensive surveys.[2,3] It would seem therefore that penicillin has contributed more than any other single factor to the steady decline in mortality observed in the past few years, granted that earlier recognition, earlier

treatment, and improved operative technique, have also exerted a favorable influence.

The early reports of combined penicillin and sulfonamide therapy were discouraging.[17] More recently, Stivelman and Kavee (1949)[18] have reported a series of 21 cases of acute putrid lung abscess, with 19 cures and one death, as contrasted to a control group of 70 patients (treated with general supportive measures but without penicillin), in which spontaneous recovery occurred in only eight.

Numerous studies have been undertaken to evaluate the most efficient method of administering penicillin. Bryson and his associates (1944)[19] are credited with the original report on penicillin aerosolization. Barach et al,[20] were among the first to attempt a clinical evaluation of the effectiveness of penicillin aerosol in bronchopulmonary infections. Fariñas and co-workers,[21] have adopted a technique developed by them for mucosography of the respiratory tract to the treatment of pulmonary suppuration. This innovation would appear to hold little advantage over the conventional methods of penicillin aerosolization. Gaensler and associates,[22] have demonstrated that parenteral penicillin does not attain detectable concentrations in the sputum by the Rammelkamp[23] dilution method. As might be expected, penicillin was recovered in the sputum following endotracheal instillation. Bryson[24] has recently shown that the bacteriostatic effect of aerosolized penicillin can be enhanced by using a detergent as a solvent for the drug.

The principle objections to the use of aerosolized penicillin are the increased incidence of sensitivity induced by contact of the drug with mucous membranes and the rather dubious concentration of penicillin which results in the diseased portion of the lung. May and Floyer,[25] and Drinker and Hardenbergh[26] have pointed out that aerosolized penicillin may not attain any higher concentration than parenteral penicillin in deep suppurative foci, since there would appear to be little stimulus for minute aerosol particles to enter a rigid motionless cavity. Such cavities could conceivably be reached by a gravitational flow of penicillin via endobronchial instillation.

The European literature contains several reports of pulmonary suppuration successfully treated by endobronchial instillation of penicillin in combination with parenteral administration.[27a,b,c,d,e] Bénard and co-workers,[27a] treated nine patients with acute or subacute bronchopulmonary abscess by this method, and reported complete clinical and anatomical recovery in eight. Complete recovery resulted from this treatment in 36 of an additional 40 cases of bronchopulmonary abscess cited in the literature. This

treatment should probably be reserved for those cases where other routes of administration appear to have failed. The undesirable side effects of this procedure include suppression of the cough reflex, irritation and edema of the vocal cords from repeated manipulation, and the ever present danger of reaction to anesthesia.

There is experimental evidence to show that in laboratory animals topical penicillin in high concentrations may be injurious to the mucous membrane of the upper respiratory tract.[28] Furthermore Eagle[29] has recently shown that bacteriostasis of certain strains of streptococci and staphylococci in vitro does not parallel increasing concentration of penicillin beyond a certain optimum level, at which point a paradoxical zone appears and bacteriostasis tends to decline.

A discussion of antibiotic therapy of lung abscess should rightfully include the newer compounds that have been derived from the genus Streptomyces which include dihydrostreptomycin, aureomycin, and chloramphenicol. Tenative recommendations regarding the antibiotic of choice in various infections and dosage schedules have appeared in the recent literature. Long[30] believes combined therapy may be the treatment of choice in severe infections; however, this is not to be construed as an endorsement of "shot gun" treatment. A penicillin reaction might be of sufficient magnitude to interdict its use and recourse to another antibiotic would be gratifying. Successful desensitization to penicillin, however, has been reported.[31]

Addendum: As a result of a recent survey, we have extended the observation period of the cases for an additional six months. In none was there evidence of a recurrence.

SUMMARY

1) The data in the literature suggest that penicillin therapy has significantly reduced the mortality of acute lung abscess. The present trend of opinion seems to favor combined parenteral and topical administration.

2) Twelve cases of acute lung abscess are reported, of these all but one were considered primary. Eleven responded to parenteral and aerosolized penicillin (in conjunction with amebacides in a single case), and of these radiographic cure resulted in 10. Residual bronchiectasis was demonstrated in but one case. One patient, treated by both medical and surgical measures, died. It was felt that the surgical procedure in no way contributed to the fatal outcome.

3) Whereas it has been emphasized that medical management is not offered in competition to surgical intervention, penicillin

therapy would appear to offer an entirely satisfactory means of treating acute uncomplicated lung abscess. Early pneumonotomy is no longer necessary as long as an abscess remains uncomplicated and uninterrupted roentgenographic regression results.

4) Penicillin therapy should be continued until complete healing has been demonstrated by roentgenologic analysis. The latter should include a bronchial mapping in every case, since a significant number of patients with symptomatic cure may have residual bronchopulmonary pathology.

5) Our experience has impressed upon us the need for thoroughly investigating every case of lung abscess for bronchogenic carcinoma, as well as bronchiectasis.

RESUMEN

1) La literatura médica sugiere que la penicillina, ha reducido considerablemente la mortalidad del abceso de pulmón agudo. La tendencia en el presente, parece favorecer la administración local y parenteral.

2) Se presenten doce casos de abceso agudo de pulmón, todos menos uno, fueron considerados primarios. Once casos respondieron a la penicillina por via parenteral y aerosol (juncto con amebiacios en un caso) y con curas radiográficos en diez casos. La bronquiectasia residual fué demostrada solamente en un caso. Un caso que fué tratado médicamente y quirúrgicamente falleció. Se creyo que el tratamiento quirúrgico, no fué responsable por esa muerte.

3) Se ha argumentado que el tratamiento médico no se ofrece en competencia con el quirúrgico; la penicilina parece que ofrece un medio de tratamiento satisfactorio no es necesaria ya, siempre que el abceso permanesce sin complicaciones, la regresión se hace evidente en radiografias periodicas.

4) El tratamiento con penicilina debe de se continuado hasta que la lesion esta curada radiológicamente. La broncografía debe ser hecha en cada caso, desde el momento que algunos enfermos son completamente asintomáticos y sin embargo se puede demostrar patología broncopulmonar residual.

5) Muestra experiencia en abcesos de pulmón, nos ha demostrado la necesidad de una prolija investigación para el cancer broncogénico y la bronquiectasia.

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The BCG Controversy*

LLOYD B. DICKEY, M.D., F.C.C.P.
San Francisco, California

A quarter of a century after the introduction of BCG vaccination, its value is still a highly controversial subject, as proved by the many recent panel discussions before medical meetings in America. The discussions have not all been carried out in the friendly tone that has characterized other debates before our local societies. There has been, however, in this vicinity, such a recent wave of enthusiasm for BCG, that within this calendar year an offer by the United States Public Health Service for an extensive BCG vaccination program has been accepted, and an offer by the same service for a mass x-ray survey of San Francisco has been refused. In other words, a third-rate method of tuberculosis control has been substituted for standard, thoroughly tried, and unfailing methods. It is time again, then, to review the facts about methods of tuberculosis control, and especially of BCG, before any discussion of its efficacy begins.

First, BCG is a living strain of low-virulence tubercle bacillus which, when inoculated into human beings produces a mild form of tuberculosis. So far, no untoward results from such inoculation have been reported in human beings, although it should be remembered that a non-virulent organism may at any time become virulent, and one with a low virulence may become powerfully so after relative innocuousness. Probably all BCG now being used has been derived from the attenuated culture originally grown by Calmette and Guerin, but as pointed out recently by Dubos,[1] it has undergone considerable variations in its career of over a quarter of a century. He states that one of the strains commonly used for immunization has caused severe disease and sometimes death when injected into mice maintained on deficient diets, and further states: "It is even conceivable that many of the classes of human beings who are most dangerously exposed to tuberculosis (for example those living under conditions of great economic distress, with inadequate food supplies) may be those least capable of responding satisfactorily to immunization procedures."

Second, there are many technical difficulties of administration such as keeping the vaccine potent, which should be mentioned. The current vaccines, as pointed out by Dubos contain from one

*From the Department of Pediatrics, Stanford University School of Medicine, San Francisco, California.

to five billion bacteria per cc., but viability tests reveal that at times as few as .001 per cent are viable at the time of injection. BCG at best is a poorly standardized vaccine, and an inadequate medium with which to study and measure immunity. There are also many records of failure to produce any immunity whatsoever, both in man and experimental animals. In Medlar's[2] most favorable results, 5 per cent of vaccinated animals died from tuberculosis when they were later infected, and as quickly as though not vaccinated. Even the production of tuberculin allergy is not an indication of immunity. The positive tuberculin reaction is an indication of the sensitivity of tissues, is not necessarily a constitutional reaction and can be produced to a certain degree with tubercle bacilli killed by heat.

Other technical difficulties worthy of note are the complications at the site of injection. The pediatrician is especially interested in these, as it may become his duty to explain the occasionally running sores, swelling of regional lymph-nodes, or any disaster, isolated or wholesale, following the use of BCG. It will, incidentally, be necessary after years of explaining to the parents the advantages of a negative tuberculin child population, to point out why we are suddenly aiming at exactly the opposite result.

Third, scientifically controlled studies from Europe are practically non-existent, and in America are few, and still contradictory. Despite this, the use of BCG in Europe has been generally accepted, where the situation in regard to tuberculous infections is in places desperate, and in no way comparable to the status in the United States and Canada. Levine[3] recently called attention to the fact that the tuberculosis mortality in children in New York City where BCG was not used, compares quite favorably with the mortality rates in Gothenberg where practically all infants exposed to tuberculosis were given BCG, but "where practically no control material was available." In the most enthusiastic reports there is only a suggestion of relationship between vaccination and decreased incidence of the disease in children over a short period of time. There are no published reports, anywhere, showing evidence of long-term benefits.

The studies under the auspices of the United States Public Health Service are the largest and the best controlled of those claiming benefits from inoculation with BCG. To state that controls "live under similar conditions" is not enough to make a scientific study, and taking as controls the groups in which the parents refuse the vaccination may lead to erroneous conclusions, as was pointed out by Levine and Sackett.[4] These investigators, in a study made on a really scientific basis, with alternate cases, showed that the efficacy of BCG can be very seriously questioned,

as their control group showed practically the same amount of tuberculosis as those inoculated. This study is naturally going to carry more weight with pediatricians in evaluating BCG than those less accurately controlled.

Fourth, the widespread use of BCG will almost entirely destroy the value of the tuberculin test, which is still the most important single item and the most reliable screen in case finding among children. This point has not been sufficiently stressed in the literature. If any widespread use of BCG be accepted, it will immediately make useless the tuberculin test, the most valuable single item in the determination of the incidence of infection, and in the sifting of cases among the young for further study. It is one of the most accurate biological tests known, although it has suffered considerably from misinterpretation from those not using it to the same extent as pediatricians do. Frequent surveys with the tuberculin test in the same area is still the best method of determining the extent of tuberculosis eradication.

The recent statements that the tuberculin reaction following BCG inoculation can be distinguished in appearance from the positive reaction following the usual infection, I do not believe. When the reaction in the skin from the injection of diphtheria toxin, of coccidioidin or histoplasmin cannot be distinguished from the reaction to tuberculin by the experienced observer, it is impossible to accept the ability of anyone—much less everyone—to reliably differentiate between the skin reaction following BCG infection and that of the ordinary tuberculin reaction, both of which are reactions to infection by different types of the same bacillus.

There are three groups of individuals who might be considered as candidates for vaccination with BCG. In the first group would be all nonreactors to intracutaneous tuberculin, and it has actually been proposed in some circles that this group should all receive the vaccine. This should not be advocated. There are now schools in some states in which not a single tuberculin reactor can be found at the grade school age level. This accomplishment, as Myers[5] has pointed out, "was made by standard, thoroughly tried and unfailing methods." BCG would be a poor substitute for such results, which can be duplicated elsewhere if the proper enthusiasms be present. Such a substitution would be comparable to using BCG at present in cattle to protect children from infected milk. Moreover, its use would eliminate the epidemiological tracing of sources which becomes feasible where incidence of tuberculin sensitivity is low.

In the second group would be the individuals working or living in a known tuberculous environment, but still nonreactors to tuber-

culin, including medical students, nurses, children of known tuberculous parents, and members of the armed forces assigned to duties in foreign countries where tuberculosis is rampant. These individuals might be offered BCG vaccine on a purely voluntary basis, but with stress still placed on the accepted methods of tuberculosis control. Even here there are objections. It would be dangerous to let anyone receiving the vaccine assume that he or she were protected to the same extent that vaccine virus protects against smallpox, and our present effective program should be in no way relaxed in regard to these individuals. The results obtained from the giving of the vaccine in this group should also later be evaluated. Of the work done among this group with BCG, Ferguson's[6] in Saskatchewan is the best known in North America, although he states that it is no attempt at a controlled study. The favorable results reported are more than matched by the reports of Myers and others[7,8] on the prevention of tuberculosis among nurses and students of medicine by the accepted and non-controversial methods and without producing large numbers of professional people with subclinical tuberculosis who may some day be working among people who are not infected.

The third group would consist of such larger sections of the population as are now being vaccinated under the supervision of the United States Public Health Service, the still nonreacting individuals of population groups heavily infected with tuberculosis. The rationale in this case is that we can offer them a cheap and easy method of dubious value on the assumption that the method of proved and accepted value, which is more costly and time-consuming, cannot be provided for them. In having sympathy for our neglected wards, the American Indians, we should also see that they are better housed, better fed, better educated, the general standard of living raised, and the tuberculosis eliminated by case finding and isolation no matter what the cost. In the giving of vaccines to all of the groups living under substandard conditions, an effort should be made scientifically to prove or disprove its efficacy. The great desirability of a large-scale, alternate-case study should be emphasized. Tuberculosis can be greatly reduced however in this group with substandard living conditions by other methods. A startling example is in a group being inoculated in San Francisco's Chinatown. During a study by myself[9] the incidence of tuberculous infection among Chinese school children in 1930 was about 40 per cent, and according to Geiger,[10] even before the project was started, the number of positive tuberculin reactors among children in the schools of Chinese enrollment, has dropped from 27 per cent in 1939-40 to 5 per cent in 1945-46.

I believe it logical, then, to say that BCG vaccination has as

yet only a small place in the armamentarium of the private physician in the United States. The inherent conservatism of the medical profession has been cited as the cause of the general lack of acceptance of BCG vaccine. It is much more likely that practitioners are not convinced of its value. Our profession accepts quickly and with enthusiasm any well-proved remedy. We may cite the examples of insulin, vitamins, sulpha-drugs, the antibiotics, and many others to prove this statement.

The technical difficulties, including that of keeping the vaccine potent, should be remembered. In its stead every effort should be made, by all the known and accredited methods, to stamp out tuberculosis in all forms at its source. We would insert confusion into the educational program against tuberculosis by trying now to convince everyone that a tuberculin reaction is desirable, when for years we have been teaching that the exact opposite is the ideal state. The use of BCG vaccine on a large scale in our child population would introduce a factor distinctly unfavorable to our efforts to find both contacts and tuberculous disease in this important age group, and the public might very well obtain a false sense of security with a resultant let-down in vigilance against this disease.

In some of the most enthusiastic reports, deaths from tuberculosis do occur in individuals who have received BCG, although presumably they would have suffered the same fate had the inoculations been withheld. At an International Congress devoted to the subject of BCG vaccination held in Paris and Lille, June 18 to 23, 1948 under the auspices of the Pasteur Institute, a set of resolutions was adopted at the closing session. Resolution 2 states: "BCG vaccination is the most effective means of preventing tuberculosis." This statement is obviously false, as it has been well established that the best method of preventing tuberculosis is by baring contact with open cases of the disease.

SUMMARY

Tuberculosis can be entirely eliminated, and has been in certain areas, by tuberculin testing, x-raying reactors, and isolation of open cases. BCG would interfere with such programs and might add the danger of large numbers of subclinical tuberculosis among the population at large. Any favorable report of BCG vaccination can be surpassed by reports with the use of accepted methods.

For the present I believe we should leave the use of BCG vaccine in the hands of the public health departments, where its use can be controlled, and the results from it properly evaluated. I stress again the urgent need of more alternate-case control studies.

Without them we cannot ever know with certainty whether BCG has any value at all.

RESUMEN

Puede eliminarse por completo la tuberculosis, como se ha llevado a cabo en ciertos lugares, mediante la prueba a la tuberculina, los exámenes radiográficos de los reactores y el aislamiento de los casos abiertos. El BCG impediría el buen éxito de estos programas y hasta podría añadir el peligro de un gran número de casos de tuberculosis subclínica entre la población en general. Cualquiera comunicación basada en la favorable vacunación con BCG puede ser sobrepasada por resultados obtenidos mediante el empleo de los métodos aceptados. Opino que, por lo pronto, debemos dejar el empleo de la vacuna BCG en las manos de los departamentos de salud pública, donde su empleo pueda ser controlado, y los resultados obtenidos adecuadamente avaluados. Quiero recalcar de nuevo la necesidad urgente de hacer más estudios que usen casos alternos como testigos. Sin ellos nunca podremos saber con certidumbre si BCG tiene valor alguno.

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Tuberculosis Control in Institutions for the Mentally Ill

EDMUND W. MILLER, M.D.
Anoka, Minnesota

The first state hospital in Minnesota was established in 1866 by the remodeling of an old hotel. From this beginning the system has grown until now there are seven hospitals for the care of the mentally ill, two for feeble-minded and one for epileptic individuals. These now have a combined capacity of about 15,000 caring for a state population of approximately 3,000,000.

In 1902 the first request was made for the construction of a separate unit for the care of state hospital tuberculous patients. This was financially provided for in 1904, and it was opened in 1906. Since that time isolation facilities have been provided at six institutions (later reduced to five), providing a total bed capacity of 604.

In 1942, Dr. H. A. Burns was appointed Head of a newly estab lished Tuberculosis Control Unit for the state's mental and penal institutions. He inaugurated a program for obtaining a chest x-ray film of every patient and employee once each year. If any suspicious x-ray film changes were apparent, repeat x-ray films and a series of three gastric lavage specimens were routinely ordered. In some institutions it was possible on clinical grounds, such as in the investigation of unexplained weight loss, to adequately consider the possibility of tuberculosis in the differential diagnosis. Active tuberculous patients, when discovered, were transferred to one of the tuberculosis isolation centers where the treatment consisted essentially of bed rest. There were several reasons for this, among them being the small number of tuberculous patients in each center, together with the latter's wide geographic separation, which militated against the employment of a clinically qualified staff to care for the tuberculous. Instead, this work was commonly assigned, as an extra chore, to a physician interested primarily in psychiatry. In spite of the obvious limitations of this program, there was some evidence that a measure of epidemiological control was being achieved.

In 1934 and again in 1944, Dr. Burns personally administered and read tuberculin tests on all of the more than 10,000 mentally ill patients. These showed in the first instance, 90.9 per cent positive reactors as compared to 73 per cent 10 years later.

For a number of years Dr. Burns advocated that one tubercu-

losis treatment center with an adequate staffing pattern be provided, which would care for all Minnesota State Hospital patients developing tuberculosis. The 1947 Legislature provided funds for this purpose but they proved insufficient. This appropriation, however, did permit plans being drawns for the remodeling, as a tuberculosis treatment center, of an existing building at the Anoka State Hospital, chosen because of its proximity to the medical centers of Minneapolis and St. Paul. The 1949 Legislature provided the additional funds needed, and work on the remodeling of this building commenced May 16, 1949. Very tragically, particularly for those of us who knew him personally, Dr. Burns' illness necessitated his taking a leave of absence a few days after the contractor actually started remodeling the building in accordance with plans to which Dr. Burns had significantly contributed of his knowledge and experience. He died July 8, 1949. His successor, Dr. A. E. Krieser, has continued the same general program for the control of tuberculosis and is, in addition, in the process of expanding the scope of his department's activities to include the epidemiological control of all communicable diseases in the mental and penal institutions of the state.

The building that is being remodeled previously housed in excess of 400 male patients. It consists of a three-story center section with two two-story wings. In the opinion of the author, and others who have studied the plans, the architect, Mr. E. D. Corwin, of St. Paul, Minnesota, did a truly remarkable piece of work in incorporating into his remodeling plans all of the services and facilities he was asked to provide. His ability to do so becomes all the more noteworthy in view of the fact that he was confronted with the limitations of an existing building originally designed for an entirely different function. His plan will provide an essentially self-contained unit with the exception of service from a central heating plant, laundry, and kitchen.

The three-story center section of the remodeled building will have on the first floor, besides the usual facilities, a visitors waiting room and adjacent room which includes lockers where visitors may store their bulky outer clothing, purses, et cetera, and properly gown and mask before entering the contaminated area; an office for the physician who will be in charge of the state-wide tuberculosis control program; a dental suite; a canteen for patient use; a beauty parlor; a barber shop; space for occupational therapy, and a common dining room for men and women patients, large enough to seat one-half of the 250 patients in the building.

On the second floor there are offices for three physicians doing the clinical tuberculosis work, a staff conference room, an x-ray room housing a 200 milliampere, general purpose x-ray unit with

spot film attachment and electronic controls, with the necessary adjuncts.

On the third floor there are dressing and locker rooms for nurses and physicians in connection with the operating suite and an operating room having a sub-sterilizing alcove and being connected by a pass window to the central sterilizing facility for the entire building. There is also space for the storage of a portable x-ray machine, that can be used anywhere in the building and more specifically in the operating room in connection with orthopedic surgery. There is also a two-room suite having a vertical fluoroscopic unit in one room and space in the other for administering pneumothorax. The balance of that floor is taken up by storage space and a medical laboratory.

The two two-story wings are identical and each of the four wards contained therein provides a nourishment kitchen, toilet, shower and bathroom facilities, clean and soiled utility room, linen rooms, and day room space. A majority of the beds are in large rooms formerly used as dormitories, now arranged in cubicles having three foot high partitions. The partitions will serve two purposes: (1) insure the patient a modicum of privacy, and (2) prevent overcrowding. Common experience in a state hospital setting is that, as the need arises, beds are pushed progressively closer together until finally it is difficult to walk between them. A duplex electrical outlet is being provided for each bed, and it is envisioned that one will be used for a light on a bedside table, while the other may be used for an individual radio equipped with earphones rather than a loud speaker.

On the two upper floors a single room is provided at the end of the ward, toward the center of the building, in which a moribund patient may be placed. Adjacent to this, situated in the "clean," off-the-ward area, there is another room for the use of relatives of such a terminal case. Incorporated in the partition between these two rooms, there are a large window and a door. Relatives may visually observe a dying patient while still remaining in a "clean" area. However, if they wish to put on a cap, gown, and mask, the door affords ready access to the patient's room.

To provide for the care of patients who have some contagious disease, in addition to their tuberculosis, a sub-isolation unit has been provided on two wards. Each unit consists of two single rooms communicating with an intermediate area having separate toilet, shower, lavatory, utility, and sterilizing facilities.

Located at strategic intervals throughout the four wards and in other areas of the building are recessed scrub-up sinks with adjacent lockers for both clean and soiled caps, gowns, and masks.

A conveniently located ambulance entrance and ramp afford

access to both the elevator and the morgue. The latter is located in the basement and provides shower, toilet, and lavatory facilities. There are also provided in this basement area a large serving kitchen with adjacent mechanical dishwashing room, an office for a dietitian, and other facilities to be described in more detail.

The problem of handling laundry from a tuberculosis unit in a central laundry serving other types of patients has been approached in the following manner. There is, on each of the four wards, an automatic washing machine for the preliminary removal of stains from soiled linen. All laundry is then dropped down a chute, which has an opening on each floor, to a collecting room in the basement. Here it is sorted and placed in a bulk sterilizer. Following the sterilizing process it is removed from the other end in a clean area and taken to the central laundry. The sorting room is equipped with ultraviolet lamps in an attempt to protect employees from air-borne infection.

In an effort to control the passage of insects from the tuberculosis building to other areas of the hospital, vit the tunnel system, a pipe line having appropriate fittings at suitable intervals has been installed. This will introduce, by momentarily opening a valve, a fog of any chosen liquid insecticide under 40 pounds of steam pressure throughout 75 feet of the connecting tunnel.

Two facilities have been provided and will function in a manner for which we were aware of no precedent. For each sex of employees, a series of three rooms are arranged so that employees going off duty will enter room Number 1, remove their work clothing and hang them in lockers where it will be exposed to ultraviolet rays for the ensuing 16 hours. They will then enter room Number 2, having shower, toilet, and lavatory facilities. They will next go to room Number 3, where they will secure their street clothing from lockers, dress, and go directly out of the building through a separate entrance servicing only this locker section. Upon going to work on their next shift, the process is reversed with the shower being omitted.

Another facility, which insofar as we know is original, is a room insulated with cork and lined with stainless steel on floor, ceiling, and walls. It is our plan to pass electrically heated food carts and tray carts, which have been on the wards and in the patients' dining hall, through this room. After having been sterilized by live steam they will be removed via a second door into the "clean" area of the serving kitchen. It is our intention to rewire these carts using glass beads on the electrical circuits in lieu of rubber and fabric insulation.

This building should, we believe, prove functionally adequate and will, we predict, significantly contribute to our over-all pro-

gram for the control of what is said to be today's most pressing tuberculosis problem, tuberculosis control in institutions for the mentally ill.

Discussion

JAY ARTHUR MYERS, M.D., F.C.C.P.
Minneapolis, Minnesota

Dr. Miller's last statement pertaining to the tuberculosis problem in institutions for the mentally ill is especially significant. Apparently this has been a most pressing problem since such institutions were first established. During the 19th century it was pointed out that more than one-third of the deaths among inmates from all causes were due to tuberculosis. Theorists speculated that mental illness predisposed to tuberculosis. They said there was something inherent in the body of the insane person which constituted an ideal soil for the development of this disease. In 1897, H. M. Bracken, Secretary and Executive Officer of the Minnesota State Board of Health, read a paper before the Conference of the State Boards of Health at Nashville, Tennessee, titled "Should the Tuberculous Insane be Isolated from Other Inmates in Our Asylums and Accomodations Provided for Them in Separate and Detached Buildings?" This was a classic in that it pointed out that the only reason for so much tuberculosis among the inmates of these institutions was contagion. Dr. Bracken emphasized the importance of finding cases of tuberculosis then in the institution and detecting others on admission and isolating them in separate buildings so they could not spread their tubercle bacilli to the other inmates. The program he laid down would be suitable for any institution today. Dr. Bracken's paper and his subsequent insistence stimulated enough interest that on two of the state hospital grounds small buildings were later in operation for isolation of tuberculous patients.

Apparently Emil Bogen now of California and H. A. Burns of Minnesota were the first, in this country, to conduct good tuberculosis surveys in institutions for the mentally ill (1934). Bogen found in a large state hospital of more than 2,000 patients the incidence of tuberculin reactors increased among the inmates according to the length of institutionalization. His study indicated that many of the inmates contracted the infection as well as illness after admission to the hospital. He ascribed this to contagion and said, "The doctrine of 'constitutional types' underlying predisposition to mental disease and to tuberculosis is not

supported by the data here presented." The same year Burns initiated a study of tuberculosis among inmates as well as personnel in state hospitals, asylums, schools for the feeble-minded and epileptics in Minnesota. Among 82 per cent of the 11,517 inmates who reacted to tuberculin, 11.2 per cent presented demonstrable pulmonary lesions. Among the 2,430 employees of these institutions, 72 per cent reacted to tuberculin, of whom 5.2 per cent had demonstrable pulmonary lesions.

These early surveys were most revealing. It was no longer a matter of estimating the incidence of primary and reinfection type of tuberculosis in institutions for the mentally ill, since actual incidences had been established by most modern diagnostic procedures. Soon surveys were conducted in various places on the Western Hemisphere including New York, California and Argentina, and serious tuberculosis problems were found nearly everywhere.

Some years ago Dr. Ray Lyman Wilbur, President of Leland Stanford University, called attention to the lag between establishment of facts and their practical application. Here is a clean-cut example in Minnesota. After Bracken emphasized the seriousness of the problem in 1897 and Burns re-emphasized it by actual survey in 1934, it was not until 1942 that a tuberculosis control unit of the State Division of Institutions was established, and not until 1950 that a satisfactory building is to be opened for adequate isolation and treatment of the tuberculous mentally ill. Thus 53 years elapsed between the publication of Dr. Bracken's paper and the opening of this hospital.

When Dr. H. A. Burns was appointed chief of the newly created tuberculosis control unit in 1942, he improvised every possible method of controlling the disease with the limited available facilities. The isolation centers which Dr. Miller has described proved effective. For example, the tuberculosis mortality rate among the mentally ill was approximately 1300 per 100,000 in 1939. There was a decrease to approximately 700 in 1948.

With the facilities Dr. Miller has described, which closely approach the ideal, one may expect a continuous decrease in the mortality rate. The continuation of admission examinations of all patients to state institutions and immediate transfer of all contagious cases to this special tuberculosis unit, as well as periodic examinations of all inmates with immediate transfer of those in whom the disease evolves to demonstrable proportion, should reduce the infections and reinfections occurring among the inmates of the state institutions to almost zero. Unfortunately, the present patient body of these institutions probably constitutes the highest tubercularized group in the state. Among any group of

adult tuberculin reactors, despite the clearness of x-ray films and total absence of evidence of clinical disease at the moment, there is certain to be a constant crop of clinical tuberculosis evolving among them. The only possible hope of preventing such a situation would be through the discovery of a drug capable of destroying tubercle bacilli in the bodies of these tuberculin reactors. As yet no such drug is available, therefore the only solution of the problem is the one now in effect, which consists of keeping the tuberculin reactors under close surveillance and as clinical lesions evolve, isolate and treat.

It was particularly pleasing to me that Dr. Miller devoted so much time to the description of his building for the isolation and treatment of the tuberculous mentally ill. It is his intention that the patients of his institution receive care, including most modern drugs, collapse therapy, pulmonary resections and everything else that is included in a most modern sanatorium for the tuberculous. He is organizing an excellent medical, nursing and social service workers staff.

Most all states have a serious tuberculosis problem in their institutions for the mentally ill. Each one should have one or more buildings, depending upon population, where these patients can be isolated and receive the best of treatment even though some patients are hopelessly ill mentally. Every effort should be made to convert the sputum so as to protect fellow-patients and personnel against contagion. Dr. Miller and Dr. A. E. Krieser, now Chief of the Tuberculous Control Unit and their co-workers have devoted a tremendous amount of time to providing the best possible facilities for the solution of the problem of tuberculosis among the mentally ill. They deserve high praise and I am sure their efforts will be rewarded by success.

For several years Dr. Otto L. Bettag, Chicago, has been Chairman of the Committee on Chest Diseases in Prisons and Institutions for the Mentally Ill of the American College of Chest Physicians. This committee has done a large volume of excellent work by way of collecting important data, setting up standards, etc., etc. This vast store of information is available to anyone who desires to initiate or improve a tuberculosis control program in such institutions.

College News

SEMI-ANNUAL MEETING, BOARD OF REGENTS

The Semi-annual meeting of the Board of Regents of the American College of Chest Physicians will be held at the Hotel Statler, Cleveland, Ohio, on Monday, December 4, 1950. The following scientific program has been arranged for Sunday, December 3.

Morning Session:

"The Modern Treatment of Cough,"
Andrew L. Banyai, Milwaukee, Wisconsin.

"Modification of Modern Thoracoplasty,"
Richard H. Overholt, Norman J. Wilson, and Francis M. Woods, Brookline, Massachusetts.

"The Pharmacology of the Pulmonary Circulation in Man,"
Henry A. Zimmerman,* Cleveland, Ohio.

Round Table Luncheons:

1. "Emphysema and Pulmonary Function,"
Edwin R. Levine, Chicago, Illinois.
2. "Indications for Resection in Pulmonary Tuberculosis,"
Richard H. Overholt, Norman J. Wilson, and Francis M. Woods, Brookline, Massachusetts, Moderators.
3. "The Clinical Application of Pneumoperitoneum,"
Andrew L. Banyai, Milwaukee, Wisconsin.

Afternoon Session:

"Recent Trends in Esophageal Surgery,"
Philip Thorek, Chicago, Illinois.

"Immunity in Tuberculosis, Including B.C.G. Vaccination,"
Jay A. Myers, Minneapolis, Minnesota.

"Surgical Treatment of Mitral Regurgitation,"
Charles P. Bailey, Philadelphia, Pennsylvania.

"Broncholithiasis and Its Pulmonary Complications,"
Earl B. Kay, Cleveland, Ohio.

7:00 P. M. Social Hour — 7:30 P. M. Dinner.
Joseph C. Placak, Cleveland, Ohio, Presiding.

Guest Speakers: Louis Mark, President of the American College of Chest Physicians; Everett F. Conologue, Dayton, Ohio, President, Ohio Chapter.

Following the speakers an X-Ray Conference will be conducted by Joseph B. Stocklen, and Sidney E. Wolpaw, Cleveland, Ohio.

Information concerning reservations for the Hotel Statler and the Round Table Luncheons will be found on page xvi in this issue of "Diseases of the Chest."

*Prize Essayist, American College of Chest Physicians, 1950.

POSTGRADUATE COURSE

The next course in Bronchoesophagology and Peroral Endoscopy under the direction of Chevalier L. Jackson, will be given at Temple University in Philadelphia, Pennsylvania, November 27 - December 8, 1950. This course has been especially planned for chest physicians and thoracic surgeons. Address all inquiries to Temple University, Department of Bronchoesophagology, Philadelphia, Pennsylvania.

Chevalier L. Jackson, President-Elect of the College was elected as President of the American Bronchoesophagological Society.

FIFTH ANNUAL POSTGRADUATE COURSE IN DISEASES OF THE CHEST, CHICAGO, ILLINOIS

The following physicians registered for the Fifth Annual Postgraduate Course in Diseases of the Chest at the St. Clair Hotel, Chicago, Illinois, on Monday, October 16, 1950:

George R. Adam, Springfield, Missouri
Frank Blanton, Richmond, Virginia
A. J. Bondurant, Springfield, Missouri*
Paul J. Breslich, Minot, North Dakota*
William P. Cappleman, Temple, Texas
Thomas Cheek, Richmond, Virginia
Siu Fan Cheng, New York, New York
T. G. Coleman, San Angelo, Texas
D. E. Cowen, Fort Morgan, Colorado
John W. Crawford, Martinsburg, West Virginia
Z. George Czaja, Chicago, Illinois
Theodore R. Dakin, Forest Park, Illinois
Merrill C. Davenport, Denver, Colorado
Joseph C. Dusard, Bedford, Indiana
Irving Freeman, Fort Howard, Maryland
David A. Goldsmith, Iron Mountain, Michigan
P. W. Hardie, Hamilton, Canada*
M. P. Harrison, Dayton, Ohio
H. N. Heinz, Kohler, Wisconsin
R. L. Hickman, Hickory Ridge, Arkansas
Boyce E. Jones, London, Kentucky**
Harold H. Jones, Winfield, Kansas
A. J. Kanter, Cincinnati, Ohio*
Michael F. Koszalka, Fargo, North Dakota
P. M. Knox, Moncton, Canada*
Joseph E. Martin Jr., Elkins, West Virginia
Joseph Mindlin, Downey, Illinois***
Richard Mills, Fort Lauderdale, Florida*
John E. Moss, Mobile, Alabama
J. A. O'Hale, Breckville, Ohio*
James J. O'Neil, Omaha, Nebraska
J. A. Patterson, Oshawa, Canada***
Carol Popp, Mount Vernon, Missouri
T. J. Rankin, Wichita, Kansas
Harry F. Rapp, Portsmouth, Ohio*
Jack Reiss, Coral Gables, Florida*
S. D. Revere, Chichasha, Oklahoma
L. W. Roe, Mobile, Alabama
Sidney Sbar, Brooklyn, New York
H. M. Schapire, Mattoon, Illinois
Eli Shulruff, Hines, Illinois
Roy K. Smith, Excelsior Springs, Missouri*
C. H. Speir, Oteen, North Carolina*
George R. Taylor, Philipsburg, Pennsylvania
William Taylor, Timmins, Canada
Albert Unger, Chicago, Illinois
Julius Venckus, Lockport, Illinois
H. A. S. Vokes, Weston, Canada
Benedict R. Walske, Fort Custer, Michigan
Carryl W. Wiggins, Oklahoma City, Oklahoma
Joseph J. Young, Appleton, Wisconsin

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*Fellow, American College of Chest Physicians.

**Associate Fellow, American College of Chest Physicians.

***Associate Member, American College of Chest Physicians.

College Chapter News

KENTUCKY CHAPTER

The Kentucky Chapter of the College held its annual meeting on September 25, 1950, in Louisville. An interesting address was given by Osler A. Abbott of Atlanta, Georgia, on "The Treatment of Emphysema." Following the scientific session a business meeting was held and the following officers were elected for the year 1950-1951:

Robertson O. Joplin, Louisville, President.
Hugh L. Houston, Murray, Vice-President.
Lawrence O. Toomey, Bowling Green, Secretary-Treasurer.

WISCONSIN CHAPTER

Approximately 300 physicians attended the annual meeting of the Wisconsin Chapter of the College at the Schroeder Hotel, Milwaukee, on Sunday, October 1, 1950.

Interesting papers were presented by Edwin R. Levine, Chicago, Illinois; Maurice Segal, Boston, Massachusetts; Howard B. Burchell, Rochester, Minnesota; Philip Thorek, Chicago, Illinois; Elston L. Belknap, Milwaukee, Wisconsin and J. Edwin Habbe, Milwaukee, Wisconsin.

The following officers were elected at a business meeting of the Wisconsin Chapter:

John Fetherston, Milwaukee, President.
Mischa Lustok, Milwaukee, Vice-President.
Leon Hirsh, Milwaukee, Secretary-Treasurer.

ROCKY MOUNTAIN CHAPTER

The Rocky Mountain Chapter of the College held its annual meeting at the Broadmoor Hotel, Colorado Springs, Colorado, September 23 and 24, 1950. The meeting was attended by 80 members and guests. The following officers were elected for the coming year:

Harold Van Der Schouw, Wheatridge, Colorado, President.
H. C. Jernigan, Albuquerque, New Mexico, Vice-President.
Bernard Yegge, Denver, Colorado, Secretary-Treasurer.

COMMITTEE ON OCCUPATIONAL DISEASES

The following members of the College have been appointed to serve on the Committee on Occupational Diseases:

Louis L. Friedman, Birmingham, Alabama, Chairman
Burgess Gordon, Philadelphia, Pennsylvania, Co-chairman
Oscar A. Sander, Milwaukee, Wisconsin, Co-chairman
Edgar Mayer, New York, New York
George R. Meneely, Nashville, Tennessee
Frank Princi, Cincinnati, Ohio
Reginald H. Smart, Los Angeles, California
C. Richard Walmer, Pittsburgh, Pennsylvania.

Book Review

Tuberculosis Reference Statistical Yearbook. Year 1948, with comparative summaries for 1947, and previous years. New York Tuberculosis and Health Association, 1949.

Over the years that the New York Tuberculosis and Health Association has been issuing its annual Statistical Yearbook, this volume has earned for itself a distinctive place in every public health library. Students of tuberculosis in particular, and of epidemiology and statistics in general, have learned to turn to the Yearbook as one of their most valuable sources of up-to-date and accurate information. They have looked forward to and welcomed each succeeding issue.

The 1948 volume not only upholds the high standards set by earlier issues, but sets a new level of achievement that may serve as a goal for editors of succeeding volumes. After some 30 pages of narrative discussion of the statistics of 1948 and the trends that have been observed in the post-war period, there follows an invaluable series of tables and charts covering over 65 pages. Forty of these are concerned with tuberculosis morbidity and mortality. Most of these deal with New York City but about 15 contain invaluable data about tuberculosis death rates in other cities and states in the United States, as well as in foreign cities and countries. The next 10 tables portray the leading causes of death in New York City and the United States while two extensive final sections give detailed data regarding the New York City tuberculosis clinic services and hospitals.

The entire volume constitutes a veritable gold mine of valuable data. Many of the data are available in no other place; others only through extensive research and long delay. In compiling this material and making it so readily available, the New York Tuberculosis and Health Association has rendered an invaluable service not alone to New York but also to all who are interested in the epidemiological control of tuberculosis. To the editor of the Yearbook, Mr. G. J. Drolet, are due special thanks and credit for the painstaking and careful work that this volume represents. It is to be hoped that in spite of his retirement the Association will continue the valuable series of Yearbooks that he has so ably pioneered.

Gaylord W. Anderson, M.D.

Comment

GODIAS J. DROLET

Godias J. Drolet has long been one of the world's outstanding contributors in the campaign against tuberculosis. He was born July 6, 1882, in Quebec, Canada. Early in his life an attack of tuberculosis took him from studies in engineering and work in a banking house. After regaining his health, he entered the field of tuberculosis and has since done much toward assisting others who have fallen ill from this disease. First, Dr. Edward L. Trudeau himself appointed Mr. Drolet to a laboratory position. From 1906 to 1908 he was statistician at the Trudeau Sanatorium under the direction of Dr. Lawrason Brown in whose office and cottage he worked. For the next eight years he served in the same capacity in the tuberculosis Division of the Bellevue Hospital, New York City. There he was with the usual group of physicians of that institution, led particularly by Dr. James Alexander Miller, who throughout life was

a close friend and practically a father to Mr. Drolet. From 1917 to 1919 he was statistician for the Commission for the Prevention of Tuberculosis in France of the Rockefeller Foundation, where he had stimulating contacts with Dr. Livingston Farrand and Dr. George Vincent. In 1919 he joined the New York Tuberculosis and Health Association, where he has been statistician for approximately 31 years. In addition, he was also until recently, assistant director of that organization. For many years he has been consulting statistician for the Tuberculosis Sanatorium Conference of Metropolitan New York.

Mr. Drolet is a charter member of the American Epidemiological Society, National Cancer Foundation and a co-organizer of the New York Diabetes Association. He is a Fellow of the American Public Health Association, the American Geographical Society, and an Associate Fellow of the New York Academy of Medicine. For approximately three decades he has been a faithful attendant of the meetings of the National Tuberculosis Association and has contributed significantly to the welfare of this organization.

As a demographer he has made numerous and valuable contributions to the literature. His writings on epidemiology of tuberculosis, public health, etc., are outstanding. His high accomplishments in statistical methods have enabled him to accurately analyze data and thus draw safe conclusions with reference to the effectiveness or uselessness of various procedures. Large numbers of tuberculosis workers from everywhere have called upon him frequently for statistical information. Through his long years of service he has made many personal sacrifices to promote the tuberculosis control movement and to be of every possible assistance to all who have called upon him for help.

The Tuberculosis Reference Statistical Yearbook, which Dr. Anderson so well reviews in this issue of "Diseases of the Chest," was developed by Mr. Drolet. He has been editor and contributor to its principal sections for many years. Throughout this time tuberculosis workers everywhere have looked to this publication for information and advice. Concerning this, it will be a shock to all to read the following sentence from Mr. Drolet's letter of March 21, 1950: "It is the last number to appear from my hand." At the same time, workers everywhere will always praise him for having developed this publication to such a high level that the Department of Health of the City of New York has taken over its preparation and publication in the future.

When Mr. Drolet reached retirement age and thus relinquished the position he has held so long, it was obvious that he still has much to contribute to the tuberculosis control movement. Therefore, on January 1, 1950, he was made consultant statistician to the New York Tuberculosis and Health Association until November 1, 1952. Moreover, he continues as consulting statistician to the Sanatorium Conference of Metropolitan New York. Mr. Drolet did not attend a medical school but he acquired much more information about tuberculosis and closely allied conditions than many who have had formal medical education. This was accomplished through intimate association not only with the physicians at Saranac Lake and Bellevue Hospital but also with many other leaders including Herman Biggs and William H. Park who taught him bacteriology, "Popsy" Welch, Linsley Williams and Charles Hatfield. For years he sat with Eugene L. Opie at the meetings of the American Epidemiological Society. Physicians like Allen K. Krause, Max Pinner, Maurice Fishberg, Benjamin Goldberg, Herbert R. Edwards, J. Burns Amberson

and George Ornstein manifested confidence in Mr. Drolet and have thoroughly appreciated his great work.

For nearly half a century he has so aligned himself in the campaign against a major disease and served so faithfully and successfully that he is now recognized as one of the world's great contributors to the control of tuberculosis.

J.A.M.

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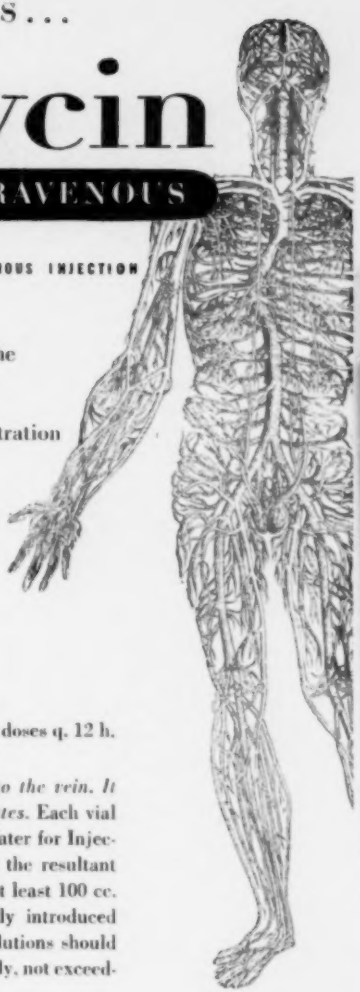

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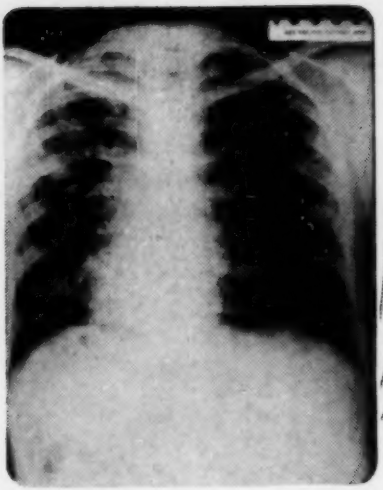

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2. *Carstensen, B.: PAS in Tuberculosis, Amer. Rev. Tuberc. 1950, 61 : 613*

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